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VOLUME 4

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CONTENTS

SECTION I

GENERAL PATHOLOGICAL METABOLISM

		PAGE
Undernutrition	*Harold L. Higgins*	3
Obesity	*Wilder Tileston*	29
Acidosis	*Donald D. Van Slyke*	51
Metabolism in Fever and in Certain Infections	*Eugene F. Du Bois*	95
Edema	*Franklin C. McLean*	153
Anaphylaxis, Hypersensitiveness and Protein Intoxication	*Warfield T. Longcope and George M. Mackenzie*	197
Disturbances of Growth	*E. V. McCollum*	239
The Metabolism of Traumatic Shock	*Joseph C. Aub*	253

SECTION II

SPECIAL PATHOLOGICAL METABOLISM

Pathological Metabolism of Diabetes Mellitus	*Rollin T. Woodyatt*	263
Disturbances of Carbohydrate Metabolism, Other Than in Diabetes Mellitus	*Isidor Greenwald*	289
Metabolism in Nephritis	*Herman O. Mosenthal*	311
Metabolism in Gout	*Joseph H. Pratt*	411
Renal Calculi Including Phosphaturia and Oxaluria	*Jacob Rosenbloom*	457
Aminoaciduria	*Jacob Rosenbloom*	475
Diaminuria	*Jacob Rosenbloom*	479
Peptonuria and Proteosuria	*Jacob Rosenbloom*	483
Bence-Jones' Protein	*Jacob Rosenbloom*	485
Alkaptonuria	*Joseph Rosenbloom and Max Kahn*	501
Cystinuria	*Max Kahn and Joseph Rosenbloom*	515
The Metabolism in Diseases of Respiration and Circulation	*Francis W. Peabody and Edna W. Tompkins*	541
Pathological Metabolism of the Blood and Blood Forming Organs	*Samuel H. Hurwitz*	553
The Metabolism in Pathological Conditions of the Stomach and Intestines	*Thomas R. Brown and John H. King*	607
The Physiological and Pathological Chemistry of the Liver	*Louis Bauman*	643
Disturbances of Metabolism Accompanying Pancreatic Diseases	*Burrill B. Crohn*	657
The Relation of Dermatoses to Metabolic Disturbances	*Walter James Highman and Jeffrey C. Michael*	693

PAGE

THE METABOLISM IN DISEASE OF THE NEUROMUSCULAR SYSTEM *Francis H. McCrudden* 707

METABOLISM IN DISEASES OF THE BONES AND JOINTS *Francis H. McCrudden* 733

THE PATHOLOGY OF METABOLISM IN INFANCY AND EARLY CHILDHOOD *W. McKim Marriott* 781

THE METABOLISM IN INFANTILISM . . . . . *Francis H. McCrudden* 813

PATHOLOGICAL METABOLISM IN PREGNANCY . . . . . *Harold Bailey* 835

DIABETES INSIPIDUS . . . . . *John R. Williams* 861

METABOLISM IN SCURVY . . . . . *Alfred F. Hess* 883

DIAGNOSIS AND TREATMENT OF BERIBERI . . . . . *Carl Voegtlin* 889

PELLAGRA . . . . . *Ward J. MacNeal* 899

THE RELATION OF DIET TO THE CAUSE AND TREATMENT OF PELLAGRA *E. V. McCollum* 911

LIST OF ILLUSTRATIONS

SECTION I

GENERAL PATHOLOGICAL METABOLISM

Acidosis

DONALD D. VAN SLYKE

FIGURE		PAGE
1.	Action of $NaHCO_3$:H_2CO_3 buffer	60
2.	Normal and abnormal variations of the $BHCO_3$,H_2CO_3,CO_2 tension, and pH in arterialized human whole blood drawn from resting subjects	69
3.	Normal and abnormal variations of the bicarbonate and pH values in arterial and venous human whole blood	70
4.	Normal and abnormal variations of the $BHCO_3$ and pH in serum or oxalate plasma	71

Metabolism in Fever and in Certain Infections

EUGENE F. DU BOIS

1.	Total metabolism of patients with typhoid fever expressed in terms of calories per square meter (Meeh's formula) per hour	97
2.	Experiments on typhoid patients with rising temperature showing an increasing heat production which outweighs the increasing heat elimination	102
3.	Typhoid patients with rising temperature, heat production remaining almost constant and in one case falling	103
4.	Typhoid patients showing fall in rectal temperature while the average body temperature is still rising	104
5.	Typhoid patients with falling temperature and rising heat elimination	105
6.	The respiratory quotients of typhoid patients on low diets examined by Kraus, Svenson, Grave and Rolly from 12-14 hours after the taking of food	108
7.	The respiratory quotients of typhoid patients on the high calory diet	108
8.	Typhoid patient, C. B., studied by von Heyden and Klemperer	110
9.	Morris S.—Temperature, body weight	111
10.	Karl S.—Temperature and body weight	112
11.	Typhoid patient Z-O, studied by Shaffer and Coleman	113
12.	Nitrogen minimum experiment of R. A. Kocher on patient with paratyphoid fever	114
13.	Temperature chart of typhoid patient, Charles N., studied by Du Bois	117
14.	Weight curve of typhoid patient who took but little food during the early part of his illness	120

FIGURE PAGE
15. Relationship of basal metabolism to temperature in various fevers . . 122
16. Results in six different fevers grouped in one chart 123
17. The lines in this chart represent a number of typical chemical reactions taken from Van't Hoff and Kanitz 124
18. Metabolism experiment by Svenson on patient with lobar pneumonia . 125
19. Patient with lobar pneumonia studied by McLean 128
20. Results obtained by McCann and Barr in tuberculosis, showing relationship of basal metabolism to temperature 133
21. Nitrogen minimum in tuberculosis as given by McCann and Barr . . 135
22. Specific dynamic action of protein in tuberculosis patients as compared with normal controls 136
23. The mechanism of the rise and fall of body temperature in tuberculosis as determined in a respiration calorimeter by McCann and Barr . . 137
24. Erysipelas patient studied by Loening 140
25. Composite curve constructed from calorimeter observations on four patients in different stages of the malarial paroxysm 141
26. Calorimeter observation made during the various stages of rising temperature 142
27. Calorimeter observation of chill following the intravenous injection of 25 million killed typhoid bacilli 145
28. Patient 27 years old with gonorrheal arthritis given 50 million killed typhoid bacilli intravenously 146

The Metabolism of Traumatic Shock

JOSEPH C. AUB

1. Oxygen content of blood in experimental traumatic shock 256
2. An example of the respiratory exchange in a cat in experimentally produced shock 258

SECTION II

SPECIAL PATHOLOGICAL METABOLISM

Metabolism in Nephritis

HERMAN O. MOSENTHAL

CHART
1. The low level of serum albumin and total serum proteins in severe nephritis with edema followed by a rise in these values with clinical improvement and loss of edema 317
2. Comparative curves of excretion of urinary nitrogen as compared with amount of nitrogen of the control periods in experimental uranium nephritis in dogs 336

Pathological Metabolism of the Blood and Blood Forming Organs

SAMUEL H. HURWITZ

FIGURE
1. Composite curve of the red blood cell count of seven dogs after splenectomy 563

FIGURE PAGE
2. Composite curve of the hemoglobin estimation of seven dogs after splenectomy 564
3. Effect of hemorrhage on the excretion of creatin, uric acid and total nitrogen in the pig 584
4. Chart showing the effect of röntgen ray and radium therapy on the basal metabolism of a patient with lymphatic leukemia 602

The Metabolism in Diseases of the Neuromuscular System

FRANCIS H. MCCRUDDEN

CHART
1. Glucose content of the blood in various conditions 721

Metabolism in Disease of the Bones and Joints

FRANCIS H. MCCRUDDEN

1. Chart showing course of typical case of osteomalacia 760

FIGURE
1. Bony tumor 762
2. Rarification of the bone 763

The Pathology of Metabolism in Infancy and Early Childhood

W. MCKIM MARRIOTT

1. The relationship between food intake and the weight curve 782

The Metabolism in Infantilism

FRANCIS H. MCCRUDDEN

PLATE
1. Dwarf. X-ray photographs of tibia, metacarpal and metatarsal bones 821
2. Cretin. Achondroplasia. X-ray photographs of metacarpal and metatarsal bones 822
3. Intestinal infantilism. X-ray photographs of metacarpal and metatarsal bones 823

Diabetes Insipidus

JOHN R. WILLIAMS

FIGURE
1. Glucose utilization test on a case of diabetes insipidus 868
2. Severe diabetes insipidus. First observation 869
3. Second observation five months later 870
4. Third observation three and one-half years later 871
5. Diagram of vertical section of brain in region of hypophysis . . . 873
6. Diagram of ventral surface of brain in region of hypophysis . . . 874
7. Curves of two hour renal studies on a case of diabetes insipidus . . 879

Diagnosis and Treatment of Beriberi

CARL VOEGTLIN

FIGURE		PAGE
1.	Severe polyneuritis due to exclusive diet of polished rice	895
2.	Same pigeon as in Figure 1, two hours after injection of vitamin	895
3.	Severe polyneuritis. Spastic type	896
4.	Same pigeon as illustrated by Figure 3, three hours after treatment	896

SECTION I

General Pathological Metabolism

Undernutrition . . . . . *Harold L. Higgins*

Water Metabolism—Body Temperature—Heat Production—Carbohydrate and Fat Metabolism—Protein Metabolism—Mineral Metabolism—Body Weight—Physiology—Muscular System—Digestive System—Circulatory System—Respiratory System—Excretory System—Nervous System—Reproductive System—Possible Duration of Fasting—Cause of Death—Breaking Fast—Therapeutics.

Undernutrition

HAROLD L. HIGGINS

CINCINNATI

In undernutrition the body gets insufficient nutriment from without to meet its needs. Included under this subdivision are conditions varying from total starvation to a failure of the body to obtain any one or several of those constituents necessary in a proper diet. The body, failing to get sufficient nutriment from the food, obtains it from the tissues, frequently more or less to its own temporary, if not permanent, disadvantage.

In surveying the possible causes of undernourishment, one has to consider the composition of the body. The body tissues consist of proteins, fats, carbohydrates and mineral elements, as the bases, calcium, sodium, potassium, magnesium, iron, and the acid elements and groups, as chlorides, phosphates, carbonates, iodine, etc.; the tissues also consist of other substances as cholesterine, and especially of water. These materials, all so essential to life and growth in one way or another, must be replenished almost constantly by the food; if it is not done, undernutrition of various degrees is practically sure to develop. The proteins of the animal body are numerous and all are very complex and different from any other anywhere; they are built up from the different amino-acids in various quantities and arrangements; the food must not only contain protein to properly meet the protein needs of the body, but it must contain protein with the proper amino-acids. The so-called vitamines, fat soluble A and water soluble B, small amounts of which are recognized as being necessary in the diet, very likely play a similar rôle. But in addition to the above constituents which are necessary for repair and growth of body tissues, there are the constituents—fats and carbohydrates—necessary to furnish the body with fuel for its activities and heat.

Thus it is apparent that undernutrition covers a very large field, and in this chapter one is naturally forced to deal with only a few phases of the subject. This chapter will therefore be limited more or less to the discussion of human undernutrition seen in absolute starvation, in starvation where only water is taken, and where the calories taken in the food are insufficient to meet the energy requirements of the body. Many problems of undernutrition are met in every-day life, and frequently, as in the late war, assume a national importance. A few such problems would

include the question of failure of individual children to grow as does the average child, the question of the underweight adult, the question of famines, etc. These present the concrete problems of undernutrition and each must be judged on its merits as to the factors involved; one must apply the general principles of undernutrition to each individual case.

Undernutrition is essentially a modified form of starvation. The physiological effects and the metabolism in both are remarkably similar. As the physiological picture of starvation is the more easily and more satisfactorily studied, it has been more extensively observed. Much of the work quoted has been work on starvation, and I have endeavored where necessary to note how it applies to undernutrition in general.

While voluntary fasting has been observed since earliest historical time, usually as a religious function or duty, it has been carefully studied from a physiological point of view only during the last thirty-five years. About this time a group of so-called professional fasters developed. Probably the best known of these was Succi. These men would fast for periods of time varying from ten to forty days, being exhibited as "sensations" to the public, who paid to see them. Perhaps in order to attract more attention from the public they consented often to observations by various physiologists and physicians. Another type of faster has also come into prominence and is one who has advocated fasting, if not as a "panacea for all ills," at least to nearly as radical extremes; the tendency has been to classify this group with the "food-faddists." The third type of faster has come from the psycho-pathological group. There have been between twenty and thirty fasts studied more or less intensively in the past thirty-five years. Fasting has perhaps been most extensively studied in Russia, where the religious fast days have made it quite common. (Pashutin, 1902.) In 1912, at the Nutrition Laboratory in Boston, Levanzin fasted for thirty-one days; an account of the fast with the scientific observations on it has been assembled in a large publication of four hundred and sixteen pages; this is probably the most extensively studied of any fast, the work being planned after a review of previous fasts. (Benedict(*d*), 1915.) Therefore, this experiment has been used for a large part of the data given in this article.

Water Metabolism

The body loses each day an amount of water varying with the external temperature and the humidity, and with the amount of muscular work done (i. e., the total energy metabolism). This loss is through the skin (sweat), the expired air, and the kidneys (urine). If no water is taken by mouth or rectum, this fluid will have to come from the tissues of the body. If there is complete starvation (i. e., neither fluid nor food intake) there will still be some water available without depleting the body store,

and this will come from two sources. One of these is the water formed in the combustion of the body material, the protein, fat or glycogen; for each atom of hydrogen would combine with oxygen to form water. The combustion of one gram of fat gives about one and one-tenth gram of water, and one gram of carbohydrate gives six-tenths of a gram of water. The other source is from the tissues themselves; the body protein exists in the cells in the proportion of about one part protein to four parts of water; for each gram of protein burned, about four grams of water are liberated; similarly, from ten to forty per cent of the weight of the fatty tissues of the body is water, and for every gram of fat burned, from one-tenth to four-tenths of a gram of water is freed. It is reported that many animals can subsist, fasting and without taking water by mouth, by reason of the fluids furnished as above, and show no evidences of water starvation. This is not true, however, of man, and the difference depends on the fact that many animals have no sweat glands, except in the paws, and thus do not lose water through the skin. Man, losing water by the skin and in greater amount by the urine, does not endure water starvation well, and a fasting man needs water to prevent early symptoms of water starvation.

Experiments on pigeons have shown that in starvation without water they died in five days, while with water they lived for twelve days. (Rubner(*d*), 1903.) Experiments on dogs show that they stand absolute starvation very well, although perhaps not so well as starvation with water. Three fasting experiments with dogs that received neither food nor water are reported, where the animals lived for forty-four, sixty and sixty-six days and then died, but not of water starvation (Awrorow).

The symptoms of water starvation are dryness of the skin, lips and mucous membranes, stupor accompanied by restlessness and irritability, and elevation of temperature. The symptoms of acute water starvation are frequently seen in pathological conditions, notably in the profuse watery diarrhea of infants, in Asiatic cholera, in patients with persistent vomiting, where no fluids are retained by mouth, and frequently in severe burns where the loss of fluid by the secreted serum is accompanied by vomiting. By merely depriving a man of water by mouth, or by giving him too little water, signs of slow water starvation appear, first with dryness of skin, hen with a tendency to desquamation leading eventually to other symptoms. Death in water starvation is from one of two causes, viz.: either the kidneys fail to eliminate the body waste products, including acids, and symptoms of poisoning occur (often acidosis), and death follows, probably by the action of these products on the vital organs, especially the nervous system; or deprivation of water from the vital organs themselves will result in death.

There is a "critical level," which represents the amount of water which must be taken in order to avoid symptoms of water starvation. This

level will vary according to the amount of water in the food taken, both molecular and potential (hydrogen), and to the amount of water excreted by lungs and skin (influenced in turn by weather, body temperature and activity). This "critical level" with the fasting man, Levanzin, was apparently between seven hundred and fifty and nine hundred cubic centimeters per day. The following table gives us some data as to the water balance in his fast:

TABLE 1

WATER BALANCE OF FASTING MAN

Day of Fast	Intake and Store Used					Output			Balance
	Intake by Mouth	Formed from Combustion of Body Material *	With Fat Tissue Burned	In Flesh (Protein) Burned	Total	Water in Urine	Water in Expir. Air and Sweat	Total	
	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams
1st	720	227	14	170	1131	630	1086	1716	585
2nd	750	211	14	202	1177	437	1188	1625	448
3rd	750	205	13	272	1240	531	1059	1590	350
4th	750	179	14	285	1228	674	779	1453	225
5th	750	182	13	250	1195	634	727	1361	-166
6th	750	166	13	244	1173	578	606	1184	11
7th	750	166	13	235	1164	496	603	1099	—65
8th	750	164	13	246	1173	557	569	1126	—47
9th	750	167	12	258	1187	575	578	1153	—34
10th	750	156	12	241	1159	535	672	1207	48
11th	900	152	12	246	1310	535	573	1108	—202
12th	900	154	12	243	1309	490	691	1181	—128
13th	900	148	11	248	1307	532	436	968	—339
14th	900	151	12	250	1313	619	540	1159	—154
15th	900	143	12	203	1258	736	442	1178	—80
16th	900	143	11	230	1284	861	578	1439	155
17th	900	140	11	212	1263	821	509	1330	67
18th	900	136	11	198	1245	633	521	1154	—91
19th	900	136	11	201	1248	705	550	1255	7
20th	900	135	11	184	1230	679	371	1050	—180
21st	900	138	11	190	1239	685	623	1308	69
22nd	900	133	11	186	1230	763	465	1228	—2
23rd	900	133	11	176	1220	537	504	1041	—179
24th	900	135	11	196	1242	728	480	1208	—34
25th	900	134	11	188	1233	692	468	1160	—73
26th	900	134	11	189	1234	706	473	1179	—55
27th	900	135	11	194	1240	631	557	1188	—52
28th	900	139	11	183	1233	634	477	1111	—122
29th	900	134	11	181	1226	676	554	1230	4
30th	900	133	11	188	1232	751	530	1281	49
31st	900	137	12	166	1215	547	625	1172	—43

* Assuming one gram body material yielded one gram water on combustion.
(Data for table from Benedict.)

Examination of the table shows that the subject lost considerable fluid during the first five days of the fast; this was coincident with and prob-

ably was caused by the depletion of the carbohydrate store of the body. Then for five days there was essentially no gain or loss of water. "On the ninth fasting day the mucous membranes of the mouth and the lips were dry. On the eleventh day the lips were desquamating (at the same time seborrhea of the scalp appeared), and this continued until the fifteenth day of the fast and did not occur again. The decrease of these signs promptly followed the prescribed intake of larger quantities of water." (Benedict(*d*), 1915.) Coincident with the change in skin condition it is noticed that water began to be retained by the body in fairly large amounts. Thus when seven hundred and fifty cubic centimeters of water were taken by mouth by Levanzin, he was showing early signs of water hunger; nine hundred cubic centimeters, however, were sufficient to overcome them.

In connection with the storage of water later in the fast, it should be mentioned that in animals both the fat and fleshy tissues of the body have a higher percentage of water on fasting. In poorly nourished children, babies with marasmus, there is occasionally an edema. This edema has been found to be associated with one of two conditions: the retention of chlorides in the body or a diet with a preponderance of carbohydrate. This latter condition has been called by the Germans "Mehlnahrschaden" (Rietschel, 1911), and the edema is usually found in undernourished children who have been fed sweetened condensed milk or a diet almost wholly of cereals and without milk. This edema is readily overcome by a change of diet. In the war there have been a number of reports of nutritional edema in certain localities, and analysis shows that the explanation is very similar to that in the marantic babies. In general, the main facts in the nutritional edemas are to be summarized as follows: (1) water retention occurs with retention of sodium chloride; (2) water is always retained with a carbohydrate-rich diet; taking away carbohydrate leads to a diminution of the preformed water in the body; (3) the water content of the body flesh and body fat is increased in fasting. Thus the fat in obese individuals has been found to contain thirteen and two-tenths per cent water, and in emaciated persons twenty-eight and two-tenths per cent. (Bozenraad, 1911.) The body flesh in emaciation also is shown to contain a higher percentage of water (Engels, 1903).

Energy Metabolism

Body Temperature.—The body temperature in starvation tends to be slightly lower than normal and to decrease slowly as fasting progresses. However, the temperature does not become what would be called pathologically abnormal until just before death. The body temperature of Levanzin at 7 A. M. each morning during his thirty-one-day fast is given in Table 2.

TABLE 2

BODY TEMPERATURE OF FASTING MAN

Day of Fast	Body Temperature °C.	Day of Fast	Body Temperature °C.
2nd	36.44	18th	36.31
4th	36.36	19th	36.40
5th	36.50	20th	36.61
6th	36.42	21st	36.04
7th	36.28	22nd	36.31
8th	36.53	23rd	35.84
9th	36.41	24th	35.78
10th	36.66	25th	36.36
11th	36.54	27th	35.98
12th	36.81	28th	36.10
13th	36.63	29th	35.92
14th	36.28	30th	35.94
15th	36.54	31st	35.96
16th	36.31	1st feeding day	36.58
17th	36.45	2nd feeding day	37.58

(Table from Benedict.)

The body temperature of a dog that died on the sixtieth day of absolute starvation is outlined in Table 3.

TABLE 3

BODY TEMPERATURE OF FASTING DOG

Day of Fast	Range °C.
1–10	38 –38.7
11–20	37.6–38.6
21–30	37.5–38.2
31–40	37.5–38.1
41–50	37.5–38.1
51–58	36.8–37.6
59–60	30.0–36.6

(Data for table from Awrorow.)

Similarly in undernutrition, unless the subject is unduly exposed to cold, the body temperature does not become pathologically subnormal. However, subjects in starvation and undernutrition experiments report a marked sensitivity to cold, and prefer to have much warmer clothing than that to which they are accustomed. (Benedict, Miles, Roth and Smith, 1919.) It is quite probable that many deaths said to be due to want of food are really the result of exposure to cold.

Heat Production.—The heat production during fasting shows a marked fall. This is shown in Table 4.

The heat production per day and also per kilo body weight becomes gradually less for about fifteen days; thereafter, the heat production is essentially constant. With undernutrition one finds a similar picture. (Benedict, Miles, Roth and Smith, 1919.) In brief, the body seems to

TABLE 4

CALCULATED HEAT PRODUCTION OF FASTING MAN. (Levanzin)

	Per 24 Hours	Per Kg. Body Wt.
	Cal.	Cal.
1st three days	1742	29.7
4– 6 days	1591	28.3
7– 9 days	1508	27.3
10–12 days	1407	26.2
13–15 days	1358	25.5
16–18 days	1292	24.9
19–21 days	1263	24.9
22–24 days	1240	24.9
25–27 days	1251	25.5
28–30 days	1258	26.1
31st day	1281	27.1

(Data for table from Benedict.)

adjust itself to its intake in calories. If a man has been taking in his food 3,500 Calories a day and his intake is changed to 2,400 Calories, the heat production will be found to change from about 3,100 Calories (the excess 400 being in non-available nutriment) to about 2,100 Calories. The heat production is proportional to the intake within certain limits. The extra heat on a high caloric diet does not come wholly from extra voluntary muscular work, although some of it does—for a man on a low diet will usually conserve his energy and be moderate in his activity. Much of the extra heat comes from extra tissue activity. The above represents essentially the theory of "luxus consumption" (Grafe and Graham(*b*), 1911).

With a fall in the caloric intake, there is usually a loss in weight, for the heat production falls slower than the food intake. A man can adjust his caloric production to equal his caloric intake down to a certain point, but not beyond. With each lowering of the caloric intake there is usually a loss of weight which, however, does not continue after the heat production has adjusted itself to the intake. The question arises "How far can the caloric intake be lowered and the heat production still adjust itself to the new level?" That would represent the critical point, which might be said to be the dividing point between nutrition and undernutrition. But on the other hand, it does not represent a level of optimum nutritional efficiency, because with this low caloric level one usually finds dissatisfaction, irritability and physical inactivity. Just what this level is varies, of course, with the weight, age, etc. For the average adult weighing sixty kg., it is about 1,600 Calories a day, while with babies it is about 60 Calories per kg. of body weight. These figures above are for individuals leading a sedentary life; to lead an active life involving muscular work, the level must be higher. In children, the necessity for growth renders the minimum caloric intake (critical point) an improper index for deciding the level of undernutrition. There are several factors which influence the

caloric levels of intake and use; weather, sex and custom are probably the most important. Women will tend to take less food than men; thus I have found that several women weighing sixty kg. took about 2,000 Calories per day, while men of the same weight took about 3,000, both doing approximately the same work. In summer we eat less than in winter. Some individuals take large quantities of food (in fact, seem "gluttons"), while others eat much less (have the "appetite of a canary").

Carbohydrate and Fat Metabolism

In fasting, the body calls upon its own tissues to furnish the energy and heat necessary for life. At the beginning of a fast, glycogen, fat and protein are available. The body carbohydrate or glycogen is the most available, for in fasting, as in feeding, the carbohydrate seems to be burned first, in preference to the fat or protein. But the glycogen store is soon depleted, as it amounts to only from fifty to two hundred and fifty grams, according to the amount of carbohydrate eaten previous to the fast (Benedict(*b*), 1907). With Levanzin in his fast, there was estimated to be a store of approximately two hundred grams, and most of it had been burned in the first three days. Experiments with animals show that some glycogen remains in the tissues for long periods during fasting. It seems likely that this small store is being continually replenished by carbohydrate formed from the body protein. It has been found in experiments with dogs that glycogen does not completely disappear until forty per cent of the body weight has been lost (Michailesco, 1914); it is also when the body has lost forty per cent of its weight that death usually occurs. No glycogen was found in the liver of a dog which had fasted one hundred and four days, dying suddenly at that time (Hawk, 1912). Carbohydrate is also found as glucose in the blood. Sugar persists in the blood throughout fasting.

After the third day, the body has to rely upon fat and protein for its supply of energy. This leads to the formation of the acetone bodies, acetone, diacetic acid and β-oxybutyric acid. These substances begin to appear in the urine, breath and blood soon after fasting begins. They are apparently excreted readily and do not accumulate sufficiently to deplete seriously the alkali reserve of the body. The amount of these substances formed vary with the individual; the obesity of that person is not necessarily the determining factor in the quantity formed. The amount of these substances vary closely with the nitrogen excreted in the urine, i. e., with the protein destruction; the explanation of this is not exactly clear, but one will recall that in fasting if more glycogen is burned less protein is used, as carbohydrate spares protein. Similar observations have been made in diabetes, for the lowered acetone body output and acidosis in the

fasting treatment is similarly associated with lowered protein metabolism. In complete starvation without water intake, there is a larger acetone body accumulation and sometimes an acidosis, for here the excretion of the acetone bodies is interfered with; this is the case also in pernicious vomiting of pregnancy and recurrent vomiting of childhood. The amount of β-oxybutyric acid in the urine of Levanzin amounted to as high as seven grams per day. In undernutrition, where the carbohydrate intake is less than fifty grams per day, acetone bodies will usually appear in the urine.

The distribution of the metabolism of Levanzin between fat, protein and cabhoydrate is given in Table 5.

TABLE 5

HEAT PRODUCED FROM DIFFERENT BODY TISSUES IN FASTING MAN

Day of Fast	From Carbohydrate	From Fat	From Protein	Total
	Cal.	Cal.	Cal.	Cal.
1st	291	1290	188	1769
2nd	178	1355	223	1756
3rd	163	1238	301	1702
4th	18	1293	315	1626
5th	64	1269	276	1609
6th	...	1267	270	1537
7th	...	1280	260	1540
8th	17	1214	272	1503
9th	57	1139	285	1481
10th	16	1144	266	1426
11th	16	1097	272	1385
12th	16	1125	269	1410
13th	15	1060	274	1349
14th	...	1117	277	1394
15th	...	1107	224	1331
16th	...	1065	254	1319
17th	...	1066	234	1300
18th	...	1038	219	1357
19th	...	1039	222	1261
20th	...	1048	204	1252
21st	...	1066	210	1276
22nd	...	1030	205	1235
23rd	...	1036	194	1230
24th	...	1038	216	1254
25th	...	1044	207	1251
26th	...	1037	209	1246
27th	...	1041	214	1255
28th	...	1087	202	1289
29th	...	1047	200	1247
30th	...	1031	208	1239
31st	...	1097	184	1281

(Table from Benedict.)

In fasting, it is the fat which meets the bulk of the body needs for calories; thus a fat person can fast ordinarily longer than one not so fat. However, most of the professional fasters were comparatively thin. After the first two days, with the depletion of the glycogen, fat becomes the

main source of energy. In practically every fast, one finds from eighty to ninety per cent of the calories come from fat, while the remaining ten to twenty per cent come from protein. But as body protein exists as flesh containing eighty per cent water, and as the energy of a gram of protein is only four-ninths of that of fat, the net result is that about two grams of body flesh is lost for every gram of body fat. This ratio persists until just before death from fasting. Then, suddenly, one finds a big increase in the protein metabolism as indicated by the nitrogen excretion in the urine. This is spoken of as the premortal nitrogen rise.

The explanation of this premortal rise has been believed to be that the fat of the body has been completely used up and therefore protein has to bear the whole brunt of the energy production in the body; thus the nitrogen output in the urine rises, the cells themselves die from too much depletion of their nitrogen content, and general death follows. The above explanation is not wholly correct, for analysis of the bodies of some animals that have had this premortal nitrogen rise and died, have shown still a small amount of fatty tissue present (Bidder and Schmidt, 1852). The theory has been advanced that an autointoxication lowers the destructive ability of the cells for fat and retards the solution of fats from the great fat depots (Tigerstedt, 1906). The general cell destruction thus seems to take place before the fat is wholly utilized (Schulz(*a*), 1897). So long as the fat produces approximately eighty per cent of the body heat in a fast, the organism shows no immediate danger of death. After the premortal rise of nitrogen has been observed, death has been forestalled by subcutaneous injections of oil (Koll, 1887) or sugar (Kaufman, 1901).

Absolute fat starvation leads to disturbances characterized by gastric and intestinal disorders, loss of appetite and eventually perhaps metabolic disturbances from want of vitamines, which are in the fat of the diet. Fat is essential for the palatability of the diet.

Protein Metabolism

The protein katabolized in fasting comes, in a large part, from the less vital organs and from the muscles. Only a few of the cells which furnish this protein are destroyed. Thus histological examination shows the muscle cells to be smaller and apparently but little decreased in number after fasting. The protoplasm is used up, but the nucleus is still essentially intact and the cell lives. This seems quite in keeping with the findings that long fasts seem to produce no permanently harmful effects upon the individual. The professional fasters seem quite as healthy as ever a few weeks after the fast is concluded. There is a record of a dog which fasted one hundred and seventeen days and then, after spending the summer on a farm, was in even better shape than before the fast, and

soon began another fast lasting one hundred and four days (Howe and Hawk, 1911).

The main facts regarding the glycogen and fat combustion come from the respiratory exchange, while those regarding the protein metabolism come from urinary examination. Many studies have been made on the nitrogen partition of the urine in starvation; the results in Levanzin's fast are given in Table 6, which summarizes the results obtained.

TABLE 6

PARTITION OF NITROGEN EXCRETED IN URINE IN FASTING MAN

Day of Fast	Total Nitrogen	Urea N	Ammonia N	Uric Acid N	Total Creatinin N	Rest N
	Gm.	Gm.	Gm.	Gm.	Gm.	Gm.
1st prelim ...	15.92	....	0.67	.....	....	....
2nd prelim...	14.48	....	0.65	.....	....	....
3rd prelim....	11.54	....	0.59	.....	....	....
1st day.....	7.10	5.68	0.41	0.112	0.48	0.42
2nd day.....	8.40	6.69	0.60	0.049	0.46	0.60
3rd day.....	11.34	9.11	0.95	0.042	0.55	0.69
4th day.....	11.87	9.03	1.40	0.044	0.54	0.86
5th day.....	10.41	7.58	1.62	0.059	0.51	0.64
6th day.....	10.18	7.36	1.68	0.097	0.52	0.52
7th day.....	9.79	7.02	1.54	0.112	0.49	0.63
8th day.....	10.27	7.45	1.65	0.108	0.50	0.56
9th day.....	10.74	7.83	1.69	0.099	0.50	0.62
10th day.....	10.05	7.44	1.59	0.118	0.49	0.41
11th day.....	10.25	7.66	1.58	0.116	0.49	0.40
12th day.....	10.13	7.43	1.49	0.154	0.49	0.57
13th day.....	10.35	7.69	1.55	0.093	0.48	0.54
14th day.....	10.43	7.69	1.59	0.125	0.44	0.59
15th day.....	8.46	6.18	1.45	0.071	0.38	0.38
16th day.....	9.58	6.71	1.94	0.099	0.42	0.41
17th day.....	8.81	5.95	1.92	0.100	0.40	0.44
18th day.....	8.27	5.70	1.80	0.122	0.41	0.24
19th day.....	8.37	5.58	1.79	0.130	0.38	0.49
20th day.....	7.69	5.36	1.58	0.115	0.38	0.26
21st day.....	7.93	5.54	1.57	0.112	0.38	0.33
22nd day.....	7.75	5.60	1.51	0.110	0.36	0.17
23rd day.....	7.31	5.01	1.49	0.097	0.36	0.35
24th day.....	8.15	5.92	1.54	0.114	0.34	0.24
25th day.....	7.81	5.43	1.52	0.098	0.35	0.41
26th day.....	7.88	5.62	1.43	0.063	0.36	0.41
27th day.....	8.07	5.90	1.38	0.089	0.35	0.35
28th day.....	7.62	5.46	1.29	0.095	0.34	0.44
29th day.....	7.54	5.55	1.32	0.101	0.35	0.22
30th day.....	7.83	5.53	1.32	0.106	0.35	0.54
31st day.....	6.94	4.84	1.24	0.122	0.32	0.42
1st feeding...	4.83	3.21	0.69	0.140	0.37	0.42
2nd feeding...	3.81	2.69	0.36	0.144	0.34	0.28
3rd feeding...	2.75	1.54	0.35	0.111	0.33	0.42

(Table from Benedict.)

In protein starvation, the protein metabolism varies with the nature of the food taken. If only carbohydrate is taken, the nitrogen output falls to a low figure; with a fat ration, the nitrogen output is higher

(Landergren, 1903). This is shown in the table for the three days following the fast, when the diet was largely carbohydrate.

In the first days of fasting, so long as there is an appreciable amount of glycogen being burned, the protein destruction is not so large as later. The nitrogen excretion then reaches its maximum and gradually falls, the fall being more or less parallel with the fall in heat production, for throughout the fast the protein furnishes about fifteen to twenty per cent of the energy.

Urea, which normally constitutes about eighty-seven and a half per cent of the total nitrogen of the urine, fell to about seventy per cent after the glycogen of the body had been depleted, and remained low for the duration of the fast. As the urea fell the ammonia rose, the sum of the two equaling in fasting about ninety per cent as compared with a normal of ninety-one or ninety-two per cent.

The ammonia nitrogen in fasting consisted of about fifteen to twenty per cent of the total nitrogen in the urine. The relatively high percentage of ammonia in the urine is doubtless to be explained on the basis of a relative acidosis. The blood in starvation has a slightly diminished alkali reserve, the alveolar air is lowered correspondingly, and there are acetone bodies being constantly formed in the body. The higher ammonia in the fasting urine is one of the body's means of defense against acidosis.

The uric acid excretion was low the first few days of the fast; this low figure may be associated with the utilization of glycogen; then the uric acid rose in amount and in general remained constant throughout the fast. The significance of the uric acid in fasting is admittedly unknown. It is lower than endogenous uric acid in feeding, and this has been ascribed to absence of glandular activity in fasting.

The total creatinine excretion (i. e., creatine and creatinine) in the urine also is apparently subject to no great variation from day to day. The tendency is to regard the amount of creatinine in the urine proportional to the amount of active protoplasmic tissues (Folin and Denis(*e*), 1913-14; Palmer, Means and Gamble, 1914). It is interesting to note that the creatinine excretion in the urine fell somewhat proportionally to the body weight. The total creatinine consists of creatinine and creatine. It has been the general opinion that, whereas creatine did not appear in the urine normally, if none were taken by mouth, it did appear during starvation. Considerable doubt has been thrown upon this opinion by recent study in the methods of analysis and much of the previous work on the creatine and creatinine portions of the total creatinine fraction of the urine (Graham and Poulton(*b*), 1914). More recent work tends to show that there is some creatine in the urine in fasting, although not so much as had previously been thought to be the case (Zeman and Howe, 1915).

The sulphur in urine comes from the protein and in fasting bears a

practically exact ratio to the nitrogen excretion, which is about fifteen to one.

Mineral Metabolism

The mineral constituents of the urine include the chlorides, the phosphates, the sodium, potassium, magnesium and calcium.

For the first fifteen days of the fast the chlorine excretion in the urine gradually became lower, then remained practically constant. Analysis of muscle tissue shows approximately seven-hundredths per cent chlorine (Katz, 1896). The following Table 7 shows the daily chlorine excretion, the amount of body flesh that has been destroyed, and the amount of chlorine contained in that flesh.

TABLE 7

CHLORINE BALANCE IN FASTING MAN

Day of Fast	Chlorine in Urine Gms.	Flesh Destroyed Gms.	Chlorine in Flesh Gms.
5	0.41	312	0.2184
10	.28	302	.2114
15	.16	254	.1778
20	.15	231	.1617
25	.18	235	.1645
30	.14	235	.1645

(Data for table from Benedict.)

Thus it is seen that the chlorine excretion in the latter part of the fast practically equals that which would be expected, were the whole amount to come from the disintegrated flesh.

A similar table (8) follows for the sodium, potassium, magnesium, calcium, and phosphates.

TABLE 8

MINERAL BALANCE IN FASTING MAN

Day of Fast	Flesh Destroyed Gms.	P_2O_5		Na		K		Mg		Ca	
		In Flesh Gms.	In Urine Gms.	In Flesh Gms.	In Urine Gms.	In Flesh Gms.	In Urine Gms.	In Flesh Gms.	In Urine Gms.	In Flesh Gms.	In Urine Gms.
		x.468%	....	x.08%	....	x.320%	....	x.0212%	....	x.0075%	....
5	312	1.46	2.64	.250	.276	.99	1.45	.066	.098	.023	.274
10	302	1.41	1.97	.242	.099	.97	1.01	.064	.071	.023	.220
15	254	1.19	1.47	.204	.109	.81	.81	.055	.070	.019	.236
20	231	1.08	1.47	.185	.065	.74	.65	.049	.052	.017	.237
25	235	1.10	1.53	.186	.065	.75	.79	.050	.055	.018	.167
30	235	1.10	1.39	.186	.053	.75	.61	.050	.052	0.18	.138

(Data for table from Benedict.)

Sodium was retained by the body, a smaller amount being excreted than was in the used flesh. Magnesium was excreted in amounts practically equal to that found in the body flesh burned. With potassium there was apparently little or no retention. Calcium and phosphates, however, were excreted in larger quantities than were present in the flesh, and this excess doubtless came from the bones. However, the excess of calcium lost is relatively small, and neither clinically nor by X-ray were there any signs of bone changes.

Body Weight

The body weight is probably the most used and the most satisfactory index of undernutrition available. In fasting, the loss of weight in practically every observed case, both in animals and men, has been similar. The loss of weight in the first few days is comparatively rapid, then less rapid each day until finally the loss becomes essentially constant. Just before death there is a sudden fall. There are many factors which play a rôle in determining the loss of body weight, most important of which are: 1. The water-balance: it is recalled that during the first days of fasting, there is a large depletion of the body fluids, which may be associated with the depletion of the glycogen. This largely explains the early loss of weight. 2. The energy metabolism: this, as has been stated, becomes less and less as the fast progresses, reaching finally a level which is practically constant. 3. Minor factors: such are loss of weight by defecation if it occurs, weather changes, activity and pathological conditions such as fever, infections, etc.

TABLE 9

Body Weight of Fasting Man

Day of Fast	Weight Kg.	Loss Kg.	Day of Fast	Weight Kg.	Loss Kg.	Day of Fast	Weight Kg.	Loss Kg.
Initial Wt.	60.64							
1st	59.60	1.04	11th	53.88	0.25	21st	50.49	0.44
2nd	58.68	.92	12th	53.56	.32	22nd	50.13	.36
3rd	57.79	.89	13th	53.45	.11	23rd	49.96	.17
4th	57.03	.76	14th	53.15	.30	24th	49.62	.34
5th	56.37	.66	15th	52.84	.31	25th	49.33	.29
6th	55.89	.48	16th	52.26	.58	26th	49.02	.31
7th	55.50	.39	17th	51.79	.47	27th	48.70	.32
8th	55.08	.42	18th	51.50	.29	28th	48.46	.24
9th	54.63	.45	19th	51.11	.39	29th	48.10	.36
10th	54.13	.50	20th	50.93	.18	30th	47.69	.41
						31st	47.39	.30

(Table from Benedict.)

With so many minor factors, which may affect the body weight, and as the first of the two major factors of itself is likely to vary, it is to be expected that the body weight curve will not have a simple mathematical

formula. Attention has been called to its being similar to hyperbola (Luciani(*a*), 1889), and while mathematically the curve is not an exact one, yet it has many of its features. For the curve shows a sharp change at the start and then tends to approach a straight line. The asymptote of the hyperbola will be a line whose direction represents the loss of weight as it becomes constant.

The weight curve of individuals who take a diet insufficient in calories is similar; here there is at first a rapid loss of weight, which is followed by a slower loss and finally by a constant loss. The asymptote of the hyperbola makes a more acute angle with the abscissa than in fasting. When the critical caloric intake is taken, then we find the body weight curve to fall at first much as before, but to soon cease to fall. The asymptote here is parallel to the abscissa. The behavior of the body weight in underfeeding or lowered caloric diet is most commonly seen in infants. It is commonly noticed that appreciably lowering the feeding of a child will result in rapid loss of weight for a day or two, followed by slower loss and then the weight tends to remain constant or increase slowly.

In summary, it may be said that the body weight falls in the case of a man getting insufficient number of calories in his diet. On a change of diet to one with fewer calories, there is usually a marked loss of weight immediately. This is especially true if the change in diet results in less carbohydrate being taken and sometimes not the case if more carbohydrate, but less calories are taken; the weight curve will fall then at a given rate, if the caloric intake is below a critical level, but the weight will become essentially constant if at or above this level.

The weight of the various organs in fasting animals as compared with control animals is given in Table 10. Analysis of the results shows that the larger part of the loss of protein is in the skeletal muscles and in the glands, while the more vital organ, the central nervous system, shows but little change. In other words, one might say that the more vital organs survive at the expense of those less needed for life.

Physiology

To understand better the true metabolism of undernutrition and to apply its affects in disease and therapeutics, it seems advisable to give an outline and discussion of the effects of fasting and undernutrition upon the physiology of the various systems in the body.

Muscular System.—The salmon, when it returns from the salt water to fresh water to breed, is fat and well developed. On its trip up the river, it does not take food, and draws on its body fat and musculature for a period of five to fifteen months, not only to meet its energy requirements but also for the development of ova or sperm. In the Rhine salmon it

TABLE 10

PERCENTAGE LOSS IN WEIGHT OF VARIOUS ORGANS IN STARVATION

Organ	Fasting Pigeon (Chassat, 1843) Fresh	Fasting Cats (Voit)		Fasting Dog (Kumagawa, 1894) Fresh Fat-free	Fasting Cats (Sedlmair, 1898)	
		Fresh	Dry		No. 1 Dry	No. 2 Dry
	%	%	%	%	%	%
Bones	17	14	..	5	19	24
Muscles (voluntary)	42	31	30	42	70	65
Liver	52	54	57	50	72	64
Kidney	..	26	21	55	58	63
Spleen	71	67	63	57	74	75
Pancreas	64	17	..	62	39	69
Testes	..	40	..	49	..	..
Lungs	22	18	19	29	30	35
Heart	45	3	..	16	55	44
Stomach	40	..	..	32	53	57
Intestines	42	18	..			
Brain / Spinal cord	2	3	..	22	1.1	..
Skin and Hair	33	21	..	28	32	44
Fatty Tissues	93	97	..	..	97	89
Blood	..	27	18	48	..	..
Esophagus	34	..	..	..	..	..

(Table from Brugsch, "Der Hungerstoffwechsel," 1908.)

has been found that, although the fish lost fifty-five per cent of their muscle tissue, yet the number of muscle fibers is apparently the same (Meischer). Similarly with animals, histological examination of the muscle tissue in fasting shows that the size of the muscle cells is much smaller, although the absolute number of them is apparently unchanged (Morgulis, 1912).

One may conclude, therefore, that in fasting and undernutrition the muscles are affected by loss of cell protoplasm rather than by actual destruction of the whole cell itself.

The undernourished man weakens under hard labor; he is not able to do prolonged muscular work, and one finds he tends to avoid it. However, he is able to perform very well feats of strength of short duration, in fact, quite out of proportion to the depletion in his muscle tissue. Thus, with dynamometer tests of the strength of the grip, but little change from normal has been found either in fasting (Benedict(*d*), 1915) or in undernutrition (Benedict, Miles, Roth, and Smith, 1919).

Digestive System.—For the first few days of a fast, the subjects complain of intermittent hunger pains. These pains are doubtless due to the rhythmic contractions of the stomach; they disappear after three or four days and do not return.

Ordinarily, during a fast, there are no feces passed voluntarily; occasionally there is a movement on about the twentieth day. Examination of

a movement obtained by sterile water enema at the end of a fast showed no change in the bacterial flora from normal. It is advisable to give enemas every two days to patients fasting for therapeutic reasons; this is of value, as the bowel movements tend to be more regular when feeding is recommenced, and the intense spasms noticed often on breaking a fast are avoided.

After a prolonged fast, there is found in the stomach only a small amount of mucus material, which is not acid. However, in a gastric test meal on a woman who had fasted twenty-four days, there was obtained fluid less rich in free hydrochloric acid and enzymes than before the fast, the hydrochloric acid secreted being proportionally less in quantity than the enzymes. The fluid was still quite capable of digesting food (Rutimeyer, 1909). Inanition does not affect seriously nor permanently the power of the digestive glands to function properly. Gastric and intestinal motility are unimpaired by fasting.

Indican was found in the urine of a dog throughout a one hundred and seventeen-day fast, and for the first fifty-four days of a second fast of one hundred and four days (Sherwin and Hawk, 1914). It has been noticed that the amount of indican in fasting in the urine seemed to be proportional to the amount of nitrogen in the urine (Gautier and Hervieux, 1907). As indol formation in the intestine from bacterial action on protein (putrefaction) is supposed to be the source of indican in the urine, some doubt has been raised as to whether this is the whole source.

In fasting, as in various pathological conditions such as diabetes and infantile diarrhea, one finds an apparent increased fatty infiltration of the liver (Mottram, 1909). This is especially marked early in fasting and where there is no fluid intake. This fatty infiltration is only apparent, rather than real, for chemical analysis shows no more fat present, but rather fat in different chemical combination (Wells(*e*), 1918). This fat begins to disappear as fast progresses, and the fat supply of the body becomes less.

Circulatory System.—Undernutrition almost invariably leads to diminished metabolism or heat production. The subject is quieter and spends less energy while being undernourished. The result is that the circulatory system apparently has less to do, and so one finds certain facts of interest: (1) the heart becomes smaller; (2) the pulse becomes slower; (3) the blood pressure becomes less, including the systolic, the diastolic and the pulse pressures.

Measurement of the size of the heart of Levanzin by percussion showed a total width of ten and seven-tenths centimeters before the fast, six and five-tenths centimeters on the thirty-first and last day of the fast, seven and five-tenths centimeters four days after the fast was broken and eleven centimeters five months later. In men taking a lowered caloric intake, a diminution of the size of the heart has also been found. Examination

of the hearts of animals after prolonged fasting show almost complete disappearance of fat (Heitz, 1912).

The pulse rate falls gradually both in undernutrition and in fasting. The figures in Table 11 give the average pulse rate of Levanzin awake in the morning before getting up. This fall in pulse rate is associated with a fall in metabolism.

TABLE 11

AVERAGE PULSE RATE IN FASTING MAN

Before fasting	72.5
First four days	71.2
Second four days	65.0
Third four days	62.0
Fourth four days	58.0
Fifth four days	57.0
Sixth four days	58.8
Seventh four days	61.0
29th to 31st-days	60.6

(Data for table from Benedict.)

A similar fall in the pulse rate of men before and after three weeks on a low caloric diet occurs as the figures given in Table 12 show.

TABLE 12

PULSE RATE IN UNDERFEEDING

Normal Diet		Reduced Diet	
Fis	56	Fis	39
Har	60	Har	44
How	58	How	40
Ham	63	Ham	42
Kim	59	Kim	48
Sch	45	Sch	33
Liv	60	Liv	39
Sne	48	Sne	40
Tho	54	Tho	39
Van	54	Van	34
Wil	57	Wil	47
Average	56	Average	40

(Data for table from Benedict, Miles, Roth and Smith.)

The blood pressure falls both in undernutrition and fasting. With Levanzin, from a figure of about one hundred and twenty millimeters Hg systolic, ninety millimeters diastolic, before the fast, it fell to about one hundred millimeters Hg systolic, eighty millimeters diastolic, toward the latter part of the fast, rising soon after the fast to the previous figure. The pulse pressure also fell from thirty millimeters Hg to twenty millimeters. The above picture is frequently seen clinically, when a low caloric feeding régime is tried in patients with arterial hypertension.

The heart, with a lower arterial tension to maintain, a lower pulse pressure to overcome, and a lower pulse rate, has considerably less work to do; with the less work, the heart would be expected to become smaller in size, which is what happens. This is probably the main explanation for decrease in size of the heart in undernutrition.

The blood itself decreases in volume during a fast or period of undernutrition; however, when one examines it, one finds essentially no change in its morphology, hemoglobin content or specific gravity. In fact, with Levanzin the only change found was an increase in the coagulation time. In undernutrition, although a man appears to be anemic, yet blood counts show a relatively normal blood picture. If, however, water is omitted as well as food, then there is an increase in the blood counts and in the hemoglobin percentage, associated with an increase in the concentration of the blood.

The literature is not unanimous as to whether starvation or undernutrition affects antibody formation (Meltzer and Norris, 1899). In typhoid fever, however, the treatment with high caloric feeding has not led to any shortening of the course of the disease. An anaphylactic reaction produced in a fasting animal is not so severe as in one which had been fed (Konstansoff, 1912).

The blood chemistry in fasting shows (1) acetone bodies, (2) a small diminution in the alkali reserve, and (3), according to some authors, an increase in the soluble proteins (Robertson, 1913). In water starvation, one finds the non-protein nitrogen increases.

Respiration.—The respiration in fasting is changed in the following particulars: (1) the alveolar carbon dioxide tension is lower, and (2) the gaseous interchange is less, because of diminished carbon dioxide production. The carbon dioxide production is lessened because there is a diminished energy metabolism and because fat predominates as the source of energy, for fat yields on combustion less carbon dioxide per unit of heat produced than carbohydrate does.

The vital capacity of Levanzin was diminished from about three and a half to two and a half liters. The respiration rate shows a tendency to increase on fasting.

Excretory System.—The kidneys in fasting, as long as water has been taken by mouth, are not harmed so as to interfere with their proper functioning in removing waste materials from the body. Albumin is found in the urine in very small amounts and there are small numbers of hyaline and granular casts. No kidney disturbance of a permanent nature has been found.

Nervous System.—The nervous system is believed to be the least affected anatomically of all the organs of the body by fasting or undernutrition. There are no definite signs of nerve degeneration or of neuritis in fasting or in undernutrition, where the diet is evenly balanced. The

reflexes during fasting and undernutrition, in spite of the increased nervous tension, tend to be depressed. With Levanzin, the pupillary, plantar and cremasteric reflexes were normal throughout the fast; the knee kick, ankle jerk and abdominal reflexes gradually diminished and were not elicited after the eleventh day of fasting. The knee kick is less irritable with reduced diet than normally.

The sensory system is essentially unchanged in fasting. The touch and pain perception is believed to be increased during fasting by reason of the loss of subcutaneous fatty tissue, making the receptors of the sensory nerve endings more easily affected by outside stimuli. The visual and auditory acuity are not appreciably changed during a fast.

In general the mental capacity is unaffected in fasting or undernutrition. Fasters have claimed that they are much more alert mentally during a fast and can think better; some qualification must be made as to these statements, however, as the subjects in making this statement have been more or less influenced by preconceived ideas as to the value of fasting. Psychological tests upon Levanzin showed essentially no impairment of mental capacity; his memory, ability to reason, and to perform word association tests was still excellent after thirty-one days. The following conclusion has been made regarding mental work in fasting: "The results show that at least they can do approximately as well, and it is not at all unlikely that some can do better, for it must be remembered that there is none of that sluggishness of the mental processes directly after eating, when the digestive processes are at their height, and there is also absence of indigestion and the after effects of alcohol and tobacco. . . . It can be stated, however, with some degree of certainty, that the complete abstinence from food for thirty-one days had little effect upon the higher mental functions, which were able to develop through practice very much as they would have done under normal conditions" (Benedict(*d*), 1915).

A group of students, getting a low caloric diet, did quite as well scholastically as a control group (Benedict, Miles, Roth, and Smith, 1919). In the war, one hears of no definite dulling of the intellect as a result of the underfeeding. This is quite in accord with the finding in animals that in fasting the nervous system seems to be the last to suffer, its weight and nutrition being remarkably well maintained, probably at the expense of other body tissues.

But when one considers the effect of underfeeding and fasting on the disposition and mental balance, then there is a different story to tell. Feeding is one of the essential routines of life—in fact, it is an instinct—and when this is affected by diminishing the food then a large amount of will power is called upon to keep from yielding to the apparent demands of the organism. This is probably no better illustrated than in mild cases of gastro-intestinal disturbances—vomiting or diarrhea—such as practically everybody has experienced occasionally. If one feels sick, almost

the first impulse is to eat something, much as the baby whose reaction in any ache or pain is to try to relieve it by food. One finds with the layman, the tendency to try first this food, then that, to relieve his symptoms and with even the professional man, the physician himself, a surprising amount of will power is required to fast. The change from a high caloric diet to a diet of fewer calories seen in changing from hard work to a more sedentary life gives one a similar sensation and a feeling of restlessness. Thus, in underfeeding and similarly on changing to a diet with fewer calories, considerable will power is required to restrain from eating more, and if more is not available, anxiety sets in. A man who is being underfed and realizes it will be under considerable mental strain. Thus during the war the irritability of the people from the lower level of feeding was the greatest difficulty that the German government had to meet.

In absolute fasting the same problem presents itself. Thus, Levanzin was under great mental strain throughout his fast; it manifested itself by periods of depression and irritability, alternating with periods of enthusiasm and elation, especially as he realized the fast was nearing an end. The hysterical manifestations to the point of mental unbalance after the fast which were brought on by the abdominal discomfort is but an indication of the strain he was under. Doubtless, the faster's emotions are somewhat different from those of the man who changes to a too low diet for the latter doubtless has the hunger pains to remind him of his condition continually and the former does not.

On return to a normal diet, however, the signs of irritability cease. The undernourished or fasting individual seems to lack initiative. He tends to spare his energies as much as possible.

Reproductive System.—Undernutrition and fasting seem to have a definite effect on that other of animal impulses or instincts, that of reproduction. In animals fasting, one finds that the ovaries and testicles become smaller (Loeb, 1917). The sex impulse and desires, notably in the male, are diminished. This was found in a group of students who had been on a low caloric ration, and the following deductions were drawn. "Any dietetic régime which, even though if affects the external appearance and performance of an individual but little, definitely lowers the tone of the sex instinct, causing one sex to take but little interest in the other, would seem to be disadvantageous to society if indefinitely prolonged and no adjustments were made in the sex instincts. Our data indicate that nature demands a rather high metabolic level for the normal functioning of sex in man. . . . Riddle and other workers find with animals that sex is closely associated with metabolism and is probably more or less dependent on the metabolic level. These investigators have shown that by modifying one they may modify the other. It is commonly believed that the sex instinct is stronger in men than it is in women. The large amount of metabolism data from this laboratory and other institutions has proved

that the metabolism of men is higher than that of women. It is not, therefore, illogical to believe that a lowered metabolism in men may reduce or even obliterate sex interest" (Benedict, Miles, Roth and Smith, 1919). It is interesting to note, as one of the factors in the Malthusean doctrine of population, that undernutrition or starvation, physiologically (and psychologically) acts to help reduce the birth rate.

Possible Duration of Fasting

Having discussed the effects of fasting on the physiology and metabolism, the question arises as to how long an individual can fast, and what is the causative factor in his death when it does occur. A man cannot survive very long without water, a time usually believed to be not over a week. If water is furnished, so that water starvation is not added to the general starvation, a man can live a considerable period of time, the duration depending somewhat upon the state of health and nutrition at the beginning of the fast. The average duration is probably between two and three months. Certain hunger strikers in Ireland recently lived about two and a half months with practically no food. The duration of life on underfeeding is more difficult to predict as so many factors enter in.

However, one can make a general rule for man and animals, that death usually occurs when the body has lost forty per cent of its body weight. Table 13 shows results obtained with various animals.

TABLE 13

Percentage Loss of Body Weight in Starvation

Animal	First Weight Kg.	Loss in Weight at Death %	Author
Dog	20.64	28	Falk
Fowl	1.95	42	Schmanski
Guinea-pig	0.67	38	Rubner
Dog	23.05	34	Schondorff
Fowl	1.00	39	Kickein
Rabbit	1.51	49	Rubner
Rabbit	2.53	44	Koll
Rabbit	2.34	41	Rubner
Fowl	1.89	34	Kuckein
Rabbit	2.08	35	Kaufman
Rabbit	2.99	32	Rubner

(Table from Lusk.)

Some individual exceptions to this have been found; thus a dog of seventeen kg. died after ninety-eight days with loss of sixty-eight per cent of its body weight (Kumagawa and Muira, 1898). In babies it has been observed clinically that the child with a feeding disturbance may lose one-

third of its body weight and still survive and recover; if more than one-third of its weight is lost, the child almost invariably dies. As would be expected, if the loss of weight is retarded by some means, the death will be delayed; thus thyroidectomized dogs have been found to live longer on starvation than normal dogs (Marinesco and Parhon, 1909).

Cause of Death

The actual cause of death is still a matter of doubt, but very probably the cause is not always the same in different cases. Death may be the result of general destruction of cellular life associated with the premortal rise of nitrogen in the urine and with the utilization of all the body fat. But a more likely cause of death is that one of the vital organs of the body fails, either from lack of nutrition or from intoxication with poisons formed elsewhere, or from destruction of its tissue in course of the general loss of body tissue.

The ultimate result of fasting and undernutrition if continued will be death; but even after the appearance of the premortal rise of urinary nitrogen, it can be staved off and health restored. On return to normal food intake, apparently, there is seldom, if ever, any permanent injury to the body.

Breaking Fast

Professional fasters have as a rule broken the fast with fruit juices and excessive carbohydrate and low protein diets. It is rather doubtful whether this is altogether desirable, for with the high carbohydrate diet there is a tendency to fermentation and gas formation in the intestines; this leads to intestinal griping and extreme colic, especially where the faster has not had a bowel movement for a long time. This was the case with Levanzin, and the abdominal discomfort combined with the mental strain of the fast were sufficient to cause him to become unbalanced mentally for a short while. On observing a breaking of fasts one will notice that, once food is taken, the craving for it is very strong and the tendency is to overeat. This must be guarded against to prevent gastrointestinal upsets.

When much food is taken after a fast, it is quite common to find sugar in the urine; this persists for only a day or two; if the amount of carbohydrate in the diet is small, however, there will be no glycosuria. The physiological explanation is probably the same as that of alimentary glycosuria for when a large amount of carbohydrate is given to a man, especially a child, accustomed to get but little, sugar usually appears in the urine.

Probably the most satisfactory food to take after fasting is a small

amount of cereal together with milk. Of course, in therapeutics, one has often to adjust the diet on breaking a fast according to the nature of the disease (as diabetes) or to the object of the fast.

One is particularly impressed by the rapidity with which the loss of weight is made up after a fast. The statement is made and in practice is usually true, that the way to gain weight is to fast, and then eat. Probably the most startling examples of this occur in typhoid fever where the body weight increases very rapidly during the period of convalescence (Svenson, 1901). The rapid gain in weight is probably to be explained on the following facts:

1—Fasting improves the appetite.
2—Allowing the digestive organs a rest, helps to overcome indigestion and then when feeding begins the digestion is improved.
3—Fasting lowers the metabolic level. Giving excess food while at this lowered level tends to cause storage of body material rather than to cause "luxus consumption." What can be added before the metabolic rate again rises, is stored, and apparently beginning to store body material stimulates the storing of more.

Therapeutics

Fasting has a place in therapeutics and in some cases is of remarkable value and usually the benefits can be explained on a physiological basis. The fasting "cure" has unfortunately, however, become a fad and been overdone by some people, who even regard fasting as a panacea. One can find several semi-popular books published which deal with the advantages of fasting (Carrington, 1908).

In gastro-intestinal disturbances fasting is one of our best therapeutic aids. This is especially to be seen in infants with vomiting and diarrhea. Apparently rest is most important in overcoming the inflammation of the mucosa of the gastro-intestinal tract. A child with indigestion will stop vomiting probably more quickly by fasting and then slowly adding food than any other way. Probably the quickest way to check diarrhea in adults, as well as in children, is by fasting. In acute gastro-intestinal disturbances, where surgical interference may be needed, fasting is a safe procedure until a definite diagnosis is made.

The Allen method of starvation in diabetes is coming more and more into favor (Joslin(*a*), 1917). Diabetics become sugar free quicker by starvation (or intermittent starvation and feeding) than in the older methods of treatment. Starvation also seems to lessen the tendency to the production of acetone bodies and to acetone body acidosis. Diabetics clinically seem to do better on a low caloric diet, often approaching or even reaching undernutrition, in having a higher carbohydrate tolerance and better gen-

eral health. This value has been ascribed by Allen in 1915, in part at least, to the rest afforded the pancreas (Islands of Langerhans).

Starvation in epilepsy has shown some remarkable results. Apparently in many cases of epilepsy, there ceases to be any convulsions so long as the patient starves. But when food is given, the convulsions begin again. I have seen a child with four to ten convulsions a day absolutely stop having convulsions so long as no food was taken. It has been reported that just before the epileptic has a convulsion, there is an increase of the urea in the blood (Dufour and Semelayne, 1920). It is likely that the reason that fasting obviates convulsions is that the body fluids have no marked changes in their chemical contents in fasting, while with food we see following each meal a cycle of chemical variations in the blood, including the nitrogenous constituents and the acid-base relationship; these changes may be a stimulus which starts a convulsion.

Permanent relief of obesity by means of fasting and undernutrition has been obtained, but sometimes the results are very disappointing. The relief requires persistent underfeeding, which unfortunately is not in keeping with the human nature, and the nervous strain associated with the treatment is often in a way pitiable. The harmful results of visceroptosis, etc., associated with loss of weight must be remembered, but probably in practice are not so important in these cases as in certain cases of enforced undernutrition.

Obesity . . . . . *Wilder Tileston*

Definition—Physiological Considerations—The Energy Requirements of the Body—The Basal Metabolism—The Effect of Food on the Metabolism—Energy Requirements on Account of Work Performed—Clinical Description of Obesity—Exogenous Obesity—Heredity—Race—Sex—Age—Symptomatology—Relation of Obesity to Other Diseases—Lipomatosis—Endogenous Obesity—Thyrogenous Obesity—Obesity of Hypophyseal Origin—Obesity of Genital Origin—Obesity and the Adrenal Gland—Adiposis Dolorosa or Dercum's Disease—The Metabolism in Obesity—Exogenous Obesity—Thyrogenous Obesity—Hypophyseal Obesity—The Treatment of Obesity—The Treatment of Exogenous Obesity.

Obesity

WILDER TILESTON

NEW HAVEN

Definition

Obesity may be defined as an excessive accumulation of fat in the body. There is no sharp dividing line at which obesity begins, but in general an increase of 15 per cent over the average weight for the height and age may be considered within normal limits, while weight in excess of this, justifies a diagnosis of obesity. Persons more than 50 per cent over weight are highly obese. Of course, it is necessary to take into account the build of the patient and the amount of subcutaneous fat, as determined by inspection and palpation.

Physiological Considerations

According to C. Voit, the human body normally contains about 18 per cent of fat. Animal fat consists of a mixture of tristearin, tripalmitin and triolein, with a small amount of other glycerides. The proportions vary not only in different animals, but in different parts of the same animal, and somewhat with the composition of the food, but in general each species has a fat of characteristic proportions. The fat of the tissues is semi-fluid at the temperature of the body.

Fat may be derived from the fat of the food, from the carbohydrates, or from the proteins. The fat in the food is digested in the intestine, and absorbed in the form of soaps. Bloor (*a*) has shown that only those fats are absorbed which can be broken down to a water-soluble (or bile-soluble) form while such substances as wool-fat and petroleum hydrocarbons (petrolatum, etc.), which are not saponifiable, are not capable of absorption. The soaps and fatty acids are resynthetized to triglycerids in the intestinal wall, and absorbed chiefly through the lymphatics, about 70 per cent appearing in the chyle. Bloor found that by the time these products of fat digestion have passed through the intestinal wall, they approximate the composition of human fat. Thus if fats with a high melting point and low

iodin number are fed, the fat in the chyle is found to have a much lower melting point and higher iodin number, and vice versa. This is accomplished by the addition of oleic acid in the former case and of fats with a high melting point in the other. Under unusual conditions, however, such as when large amounts of foreign fat are fed to a starving animal, the fat may be deposited unchanged, as shown by Munk and others in experiments with mutton fat, linseed oil, etc.

That carbohydrate may be converted into fat is a well known fact, which has been proved by feeding experiments. The situation where this change takes place is not yet known. An interesting effect of such conversion on a large scale is the raising of the respiratory quotient, which may go well above unity under exceptional conditions, as in marmots just before hibernation (Pembrey). This is due to the conversion of a substance rich in oxygen to one poor in that element, with the giving off of CO_2.

Protein may serve as a source of fat, as has been shown by feeding experiments in which large amounts of meat were given. This probably results from the conversion of the carbohydrate portion of the protein molecule to fat. To what extent this takes place under ordinary conditions has not been ascertained.

The bulk of the fat of the tissues is ordinarily derived from carbohydrate, which usually furnishes two-thirds of the energy derived from the food. Fat comes next, while protein provides only a negligible quantity.

Fat is deposited in health chiefly in the subcutaneous tissues, to a lesser degree about the abdominal viscera, serving as a padding to keep the organs in place. In obese subjects it is also largely deposited in the abdominal cavity, about the viscera and in the omentum and mesentery and retroperitoneal tissues, also about the heart, which may show a marked degree of fatty infiltration.

Fat is not ordinarily deposited in the liver to any great extent, the fat content of the normal liver being six per cent. In starvation and cachexia, however, the amount rises considerably. There is an antagonism between glycogen and fat deposit, for if carbohydrates and fat be given together to a starving animal, the liver fat does not increase, but glycogen is retained, while in obesity, on the other hand, the fat content may be increased to a certain extent, at the expense of the glycogen, as indicated by the researches of Means.

Following the law of the conservation of energy, foodstuffs must be stored in the body whenever the amount of energy introduced with the food, as expressed in calories, is in excess of the energy consumed. Since the ability of the body to store carbohydrate and protein as such is limited, an accumulation of fat is bound to occur if the excess of income over outgo is long continued. This disproportion may be due either to

excessive eating, or to too little muscular activity, or more usually to a combination of both factors. There is no evidence that mental exertion leads to an increased consumption of energy. There remain a few instances, probably only a small fraction of one per cent, in which a lowered basal metabolism is responsible, wholly or in part, for the obesity, though even here it is of course necessary that the calories taken in should be in excess of the consumption.

The normal person following his natural appetite, takes, according to a universal biological law, just what food he needs, and his weight, with slight variations, remains constant. Under the conditions of modern life, however, it often happens that people overeat, or continue their old habits of eating after changing from an active to a sedentary form of life. The result is obesity. How small a daily excess in the food will, if long continued, lead to corpulence is shown by a calculation of von Noorden(*a*), who assumes a daily excess consumption of 200 calories, which is contained in 10 ounces of milk, or two large oranges. This would lead in the course of a year to a deposition of 7.8 kg. of fat, or allowing for the water content of fat tissue, an increase in weight of 11 kg. (24 lbs.).

The Energy Requirements of the Body

The Basal Metabolism.—By this term is understood the amount of energy consumed by the body when completely at rest and in a fasting condition, at least 14 hours after the last meal. If this is reckoned as calories per square meter of body surface, it is practically constant for healthy men and animals of all sizes, as first shown by Rubner(*a*). The calory production per unit of weight or height is also fairly constant for persons of average build, but is not a reliable criterion in the case of fat or very thin individuals.

Until very recently the old Meeh formula has been used to determine the surface area. This is based on the law that the surfaces of similar solids are proportional to the $\frac{2}{3}$ power of their volumes. Meeh made actual measurements of the surface area of a number of persons, and using the weight in kilograms to represent the volume, found that the $\frac{2}{3}$ power of the weight, multiplied by a constant (12.312) gave results which agreed within seven per cent with his measurements. Subsequent work has developed the fact that this formula is fairly accurate for individuals of average build, but not for those of unusual shape, giving results which in the case of the obese are much too high (as much as 40 per cent).

Du Bois and Du Bois have recently developed a formula based on linear measurements of the various parts of the body, which gives a very close approximation of the surface area, as determined by actual

measurements. They have also devised a method for determining the surface area from the weight and height. The formula is:

$$A = W^{0.425} \times H^{0.725} \times 71.84,$$

where A = surface area, W = weight in kilograms, and H = height in centimeters. They have constructed graphic curves from which the surface area can be calculated at a glance, given the weight and height. The two formulas give about equally good results, with an average error of only 1.5 per cent as compared with actual measurements of the surface area, and a maximum error of 5 per cent. The average error by the Meeh formula is estimated by them at 15 per cent.

When the surface area is calculated by one of the DuBois formulas, the normal basal metabolism of the adult male is found to be 39.7 calories per hour per square meter. It varies with age and sex, as is shown by the following table taken from the paper by Aub and Du Bois.

TABLE I. CALORIES PER SQUARE METER PER HOUR

(Height-Weight Formula)

Age	*Males*	*Females*
12-14	49.9*	..
14-16	46	43
16-18	43	40
18-20	41	38
20-30	39.5	37
30-40	39.5	36.5
40-50	38.5	36
50-60	37.5	35
60-70	36.5	34
70-80	35.5	33

* This figure does not appear in the original table, and was taken from DuBois' article, Arch. Int. Med., 1916, xvii, 887-901.

The basal metabolism in children has not been studied in enough cases to establish averages, but from the work already done it is apparent that it is low in early infancy (30 calories) rising rapidly during the first year to about 50, and reaching a maximum of 55 to 60 Cal. per sq. m. per hour at some time between the ages of 1 and 2 years. (According to Benedict and Talbot, the calories per square meter vary considerably in young children, but more constant curves are obtained by calculating the calories per kilo body weight.) After this there is a gradual fall with a temporary rise just before puberty. As may be seen in the table, the basal metabolism falls gradually with advancing years, and is about 7 per cent lower in women than in men.

Harris and Benedict have recently made a study of the basal metabolism of a large number of normal persons, and have devised formulas by which the normal metabolism of adults may be closely predicted, given the age, sex, weight, and stature. They publish multiple prediction tables giving the expected metabolism for any adult according to these data.

Means and Woodwell discuss the comparative accuracy of the various methods of calculating normal basal metabolism. They conclude that the average deviation of the predicted from the actual metabolism is essentially the same as calculated by the Du Bois height-weight chart, the Harris-Benedict prediction tables, and the Dreyer body-weight formula, and suggest that the Du Bois method be followed, since it is already in common use.

The Effect of Food on the Metabolism.—The taking of food raises the metabolism materially. The ingestion of protein in particular has a very striking effect in this direction, which is called the specific dynamic action of protein. Carbohydrates and fat have a similar, but lesser effect. According to Magnus-Levy(*k*), the increase amounts to 17 per cent of the caloric value of the food in the case of protein, 9 per cent for carbohydrate, and 2½ per cent for fat. The specific dynamic action of protein is very thoroughly discussed by Lusk(*e*), to whom we owe much of our knowledge on this subject. The extra heat production on a mixed diet amounts to about 14 per cent of the basal metabolism, so that this much extra must be taken if the body is to be maintained in equilibrium in a state of rest.

Energy Requirements on Account of Work Performed.—Muscular exercise increases the metabolism more than any other factor. Thus it has been found that moderate exercise increases it about three times, and very severe exercise as much as nine times. It is usually stated that a man requires about 36 calories per kilo if doing light work, and from 45 to 50 calories per kilo if doing heavy work, or about 2500 calories and 3500 calories respectively for a person weighing 70 kilos.

Clinical Description of Obesity

Obesity in general may be divided into two main groups, the exogenous and the endogenous.

Exogenous obesity is the ordinary form, in which the condition is simply the result of an excess of intake over outgo in an otherwise healthy organism.

In the endogenous form there is usually, perhaps always, an alteration of function of one or more of the endocrin glands, which appears to be the cause, either directly or indirectly, of the obesity. In most instances the basal metabolism has been found normal, in a few it has been found definitely decreased. There is a theoretical possibility that an endogenous form may exist independent of disease of the endocrins, with lowered metabolism resulting from a primary lessened activity of the body cells, but such a type has not been proved to exist.

Exogenous Obesity

This is the ordinary form of adiposity, the Mastfettsucht of the Germans, and constitutes probably ninety-nine per cent or more of the cases met in practice.

Heredity.—A history of obesity in other members of the family is obtained in about seventy per cent of the cases. Since, however, the metabolism is normal, it is evident that the obesity is not inherited, and a careful inquiry will show that family habits of eating, possibly combined with the inheritance of a phlegmatic disposition, account for the condition.

Race.—Certain races show a large incidence of obesity. This is to be attributed entirely to their manner of life.

Sex.—Obesity is much more common in women, owing no doubt to their less active form of life, and to the influence of repeated pregnancies, during which, owing to a popular misconception, overeating is usually encouraged.

Age.—Obesity develops most often in women during the period from 30 to 40 years, and in men between 40 and 50. The earlier incidence in women is due mainly to the influence of child-bearing and lactation, with the accompanying overeating and lack of exercise. The menopause, contrary to a common belief, exerts little influence, the weight remaining stationary or decreasing quite as often as it increases at this epoch.

Less often the onset is in childhood. A not infrequent type is that in which obesity develops around the age of ten years, to disappear, without treatment, after puberty is established.

Symptomatology.—So long as the accumulation of fat is of moderate proportions, no symptoms result. With a high degree of obesity, however, and with lesser grades in the presence of serious disease of the heart and circulation, the condition is more serious.

The Circulation. The chief danger lies in the effect on the heart. As is well known, the weight of the heart is proportional, not to the body weight, but to the total weight of the voluntary muscles. The heart in the obese during exertion is put to a greater strain on account of the greater mass to be moved, and not being as a rule hypertrophied, must respond with a greater proportion of its reserve force than is normally employed. With increasing weight, and decreasing muscular power owing to restricted exercise, the disproportion becomes greater, until finally a stage of cardiac dilatation and decompensation is reached. Contributing factors are impeded motion of the diaphragm due to distention of the abdomen by fat, and in extreme cases fatty infiltration of the cardiac muscle, which may be so extensive that the contraction of the fibers is

interfered with. Cases of obesity complicated by hypertension, valvular lesions or myocardial disease are especially prone to decompensation.

It is not surprising therefore that the obese suffer from shortness of breath and palpitation on exertion, and in the later stages often develop the signs of cardiac insufficiency.

Hypertension and arteriosclerosis are common among the fat, and an important place is usually assigned to overeating among the many factors leading to these obscure conditions. There are some statistics in favor of this view. Thus B. Moses reported from the records of a life insurance company that while, in general, death from apoplexy occurred in six per cent, in the case of the obese the rate rose to 11 per cent. Once well established, the hypertension rarely yields to a reduction cure.

The Lungs. Owing to the impeded respiration, obesity is apt to retard the recovery from pulmonary infections, especially bronchitis, and it may happen that cases which have resisted other forms of treatment, lose their cough rapidly when their weight is reduced by diet.

The Alimentary Tract. Fat people often suffer from carbohydrate fermentation, with distention, colicky pains, flatulence and belching. Constipation and hemorrhoids are common.

The Liver. It is often stated that the liver is enlarged in obesity as a result of fatty infiltration. This is contrary to the experimental evidence, which shows that the liver contains more fat in starvation than in the well-nourished, and that if both carbohydrate and fat are given to a starving animal, glycogen, not fat, is deposited in the organ. The fatty infiltrated liver is encountered post mortem chiefly in diseases associated with cachexia, with the exception of the fatty cirrhotic liver, in which it is fair to conclude that toxic influences are at work. In Cushing's case of hypopituitarism with marked fatty infiltration the organ was not enlarged. Clinically one meets enlargement of the liver in the cases with cardiac decompensation or cirrhosis.

The Pancreas. The relationship of obesity to diabetes is discussed farther on. In the case of a rare disease, acute pancreatic necrosis, obesity is an important predisposing factor, the extensive infiltration of the pancreas with fat facilitating the spread of the necrosis.

The Kidneys. Obesity as such has no direct influence on the kidneys, but the incidence of chronic nephritis among the obese past middle age is quite high. Von Noorden(*o*) found this disease in 20 per cent of his cases of marked obesity, and obesity was a factor in "at least a third" of his cases of chronic nephritis.

The Sexual Apparatus. In the male impotence is not very uncommon, in the absence of endocrin disturbance; it is usually curable by reduction of the weight. Azoöspermia has been observed in a few instances, in which, however, disease of the endocrin glands was not excluded.

In women disturbances of menstruation are common, usually in the form of irregularity and decreased flow. The occurrence of amenorrhea should arouse suspicion that the endogenous form of obesity is present.

The Nervous System. A tendency to drowsiness is a frequent symptom among the very obese, and may lead to great inconvenience. The fat boy in "Pickwick Papers" is a familiar example. The tendency to apoplexy in later life is explained by the associated hypertension and arterial change.

Relation of Obesity to Other Diseases.—*To Diabetes.*—It has long been known that obesity favors the development of diabetes in those who are predisposed to this malady. The association may be explained by the overtaxing of the function of the pancreas owing to the excessive consumption of carbohydrates. The importance of obesity in this connection has been recently emphasized by Joslin(*b*), who states, on the basis of the analysis of 1000 personal cases, that "the individual who is overweight is at least twice, and at some ages forty times as liable to the disease." And again, "it is rare for diabetes to develop in an individual above the age of 20 years who is habitually underweight." It seems clear that, though the predisposition to diabetes is not affected by diet, the outbreak of the disease may be prevented by the prophylaxis and dietetic treatment of obesity.

Gout. The relationship to gout is somewhat similar. Gout is due to an abnormality of the purin metabolism, often inherited. Excessive consumption of protein food and of alcohol appear to be the chief predisposing factors. Gouty patients usually overeat in regard to fat and carbohydrates also, hence the association with obesity. It should be noted however, that where gout is a result of lead poisoning the sufferers are usually thin.

Other Detrimental Effects of Obesity. It has been shown that fat is the least resistant to infection of all tissues, and heals the slowest. The distention of the abdominal cavity with fat is an obstacle in abdominal operations, and the impaired vitality of the obese increases the post-operative mortality. Hence the fat person is obnoxious to the surgeon. The mortality from the acute infectious diseases is notoriously higher among the obese.

Lipomatosis

This condition is distinguished from obesity by the fact that the fatty deposits show a peculiar distribution; it may or may not be associated with general adiposity. There are three main varieties: circumscribed nodular lipomatosis; diffuse symmetrical lipomatosis, and lipodystrophia progressiva. Dystrophia adiposogenitalis and obesity following castration belong more properly to obesity proper, while adiposis

dolorosa occupies a doubtful position. Border-line cases are not infrequent, and are difficult to classify, as emphasized by Lyon, who discusses the whole question at length.

(1) *Circumscribed nodular lipomatosis.* This condition is characterized by the presence of lipomata of the ordinary variety. Though it may be associated with the rarer types of obesity and lipomatosis, it is so common apart from these that there is probably no causal connection, and it should therefore be classified with the benign tumors.

(2) *Diffuse symmetrical lipomatosis.* This form differs from the preceding in that it is chiefly confined to males, while the ordinary lipoma is much more common among women, and in the fact that the fatty masses are seldom encapsulated. The fatty deposits are most commonly situated in the neck, constituting the "fatty neck" of Madelung, but are sometimes symmetrically placed on the trunk and extremities, especially in relation to the muscles, and always to the exclusion of the face, hands and feet. The etiology is obscure.

(3) *Lipodystrophia progressiva.* This exceedingly rare disease is characterized by a progressive and profound atrophy of the fatty tissues of the face and upper part of the body, often associated with fat deposit about the buttocks and thighs. The cause is unknown.

Endogenous Obesity

Endogenous obesity may be defined as obesity dependent upon disordered function of one or more of the endocrin glands. It is rare in comparison with the ordinary form.

(1) **Thyrogenous Obesity.**—The thyroid gland is usually more or less enlarged, but in the absence of histological examinations little more can be said. The obesity usually sets in early in life, and may be due to inherited tendencies. It is very resistant to diet, but yields to thyroid therapy. Occasionally obesity develops in connection with thyroiditis, especially after the acute infectious diseases, and in syphilis. Lesser grades of thyroid insufficiency are accompanied by a basal metabolism which is within normal limits. In such cases exogenous factors are often at work (overeating, etc.), and hypofunction of the thyroid may merely create a predisposition. In a few instances a well-marked lowering of the basal metabolism has been demonstrated; these cases are distinguished from myxedema by the lack of the usual symptoms of the latter condition, and by the fact that fat, not mucin, is deposited.

(2) **Obesity of Hypophyseal Origin.**—Fröhlich was the first, in 1901, to call attention to the association of obesity of a peculiar form and dysgenitalism with a lesion of the pituitary. The discovery that these changes are due to diminished functioning of the gland, or hypo-

pituitarism, was made by Cushing(*c*), to whose work we owe so much of our knowledge of this subject.

The original Fröhlich's syndrome, also called dystrophia adiposogenitalis, included undergrowth of the skeleton. Further experience has shown that another type exists, characterized by skeletal overgrowth.

As emphasized by Cushing, hypopituitarism may result from a primary hypoplasia of the gland, from hemorrhage, inflammatory processes (especially syphilis) or from tumor. A tumor of the interpeduncular region by pressure on the gland, or by obstructing the discharge of the secretion of the posterior lobe through the infundibular stalk, may lead to the symptom-complex. Furthermore, internal hydrocephalus, if of a high grade, may by dilatation of the third ventricle lead to a similar obstruction. Hence a condition of "cerebral adiposity" has been described, due to hydrocephalus without a direct lesion of the hypophysis.

Obesity of hypophyseal origin often reaches high grades, and may come on with great rapidity. It is characterized in the male by the peculiar distribution of the fat, which is deposited especially about the breasts, in the suprapubic region, in the abdomen and about the hips and buttocks. This distribution, with the broad pelvis, knock-knees, and feminine distribution of the pubic hair, gives a very characteristic appearance to the patient. In the case of women with hypopituitarism the fat distribution is of a similar type, but since this is usual in the ordinary form of obesity in this sex, the appearance is less striking.

Cushing has called attention to an extensive fatty infiltration of the viscera, especially of the liver.

The genital changes are striking and important. In both sexes there is a hypoplasia of the gonads, associated with lack of development of the secondary sex characters. In the male the testes are small, the penis underdeveloped and the pubic hair is of the feminine type. In the female the ovaries, uterus and external genitalia remain in an infantile stage, and the pubic hair is sparse. These changes are due to imperfect development of the interstitial cells of the testis and ovary, which results in defective internal secretion. The genital changes are therefore in the case of hypopituitarism a secondary effect due to the loss of some substance elaborated by the pituitary which stimulates the growth of the interstitial cells of the gonads.

The character of the genital changes depends upon the period at which hypopituitarism sets in. If the onset occurs in childhood, lack of development of primary and secondary sex characters occurs, with consequent sterility; if in adult life, amenorrhea, impotence and atrophy of the gonads take place, while the external genitalia remain unaltered, except for diminution of the pubic hair.

Other signs of pituitary insufficiency (posterior lobe) are lowering of

the body temperature, slow pulse rate, dryness of the skin, increased sugar tolerance and drowsiness.

The clinical picture is modified in cases due to tumor by the presence of the signs and symptoms of this condition. Localizing signs may be present, such as bitemporal hemianopsia. Enlargement or deformity of the sella turcica usually occurs in connection with tumor of the hypophysis, and may be demonstrated in life by the Roentgen ray. A normal or an abnormally small sella may be found in connection with primary hypoplasia of the gland.

The diagnosis of hypopituitarism should be suggested by the occurrence of obesity in the male with dysgenitalism and drowsiness, or in the female when amenorrhea, sterility and an infantile condition of the sexual organs are concomitant. In such cases a careful neurological examination should be made, including x-ray pictures of the sellar region.

(3) **Obesity of Genital Origin.**—Castration in the male, as shown by Tandler and Grosz, leads to precisely the same changes in the fat distribution as hypopituitarism, with pubic hair of the feminine type. The epiphyses do not unite and an overgrowth in the bones of the extremities takes place. A secondary enlargement of the pituitary ensues. General obesity is frequent, but not invariable. The effect of castration in the female, if performed in childhood, is to prevent the development of the uterus and of the secondary sex characters. Partial eunuchism, a condition similar to that following castration, is met with occasionally as the result of destructive disease of the gonads occurring before adolescence.

The distribution of the fat differs also in another respect from that of ordinary obesity; it infiltrates the voluntary muscles. This is the reason for castration among cattle, for it improves the beef.

(4) **Obesity and the Pineal Gland.**—A high grade of obesity may be associated with tumors of the pineal gland, as shown by Marburg. Such cases are characterized by precocious sexual and genital development, skeletal overgrowth, and the signs of a tumor in the region of the corpora quadrigemina. Cushing points out that the adiposity might well be due to the accompanying hydrocephalus with obstruction of the pituitary discharge.

(5) **Obesity and the Adrenal Gland.**—A very similar clinical picture has been described in a rare type of adrenal tumor occurring in childhood, in which there are obesity, skeletal overgrowth, pilosity, premature sexual development and mental dulness. The symptoms are apparently due to overactivity of the adrenal cortex, for in one case only a simple hyperplasia of the gland was found.

At this point a curious polyglandular syndrome should be mentioned, in which enlargement of the salivary glands, and sometimes of the lacrimal glands, is a conspicuous feature. The condition thus resembles the Miku-

liez syndrome, but differs from it in the involvement of the endocrin glands, and in the fact that in Hämmerli's case, the only one coming to autopsy, a simple hyperplasia of the salivary glands was found. In addition to the salivary glands, the thyroid was involved in most of the cases, and dysgenitalism was frequent. The hypophysis was occasionally affected. Signs of status thymolymphaticus were frequently associated. Syphilis was noted in several instances as an etiological factor.

In no less than 11 of the 26 cases reported by Berthon, Mohr and Nagel, obesity was present. It is probably ascribable to disease of the thyroid. The association with dysgenitalism is interesting, in view of the interrelationship between the salivary glands and the gonads. The question whether the salivary glands have an internal secretion is still an open one.

(6) **Adiposis Dolorosa or Dercum's Disease.**—In 1888 Dercum described a new condition, to which he gave the name adiposis dolorosa. It is characterized clinically by four cardinal symptoms: (1) adiposity, (2) tenderness and pains, (3) asthenia and (4) psychic changes.

The adiposity in typical cases shows a characteristic distribution. Large pendulous masses of fat, having a worm-like feel, develop especially in the upper arms, the thighs, the inner aspect of the knees, and in apron-like form on the lower abdomen. Deep furrows separate these masses from the surrounding parts. Excellent photographs may be found in the second article of Dercum and in that of Lyon.

More rarely, as emphasized by Vitaut, the fat occurs in the form of (a) nodular circumscribed lipomata, or (b) diffuse localized fat deposits, the remaining parts being free from fat accumulation. Various combinations of these three types may be met with.

The fat deposits, both large and small, are exquisitely tender, and are often the seat of spontaneous pains of a neuralgic character. Sometimes there is pain along the course of the larger nerve trunks. Paresthesiæ are common, and occasionally there are localized areas of anesthesia. All of these signs, including the tenderness, are probably ascribable to a neuritis affecting the nerve fibrils in the subcutaneous fat, which has been demonstrated histologically by Dercum and others.

The muscular weakness may be profound, resembling in pronounced cases that seen in Addison's disease, and at once suggestive of disease of the endocrin glands. It is incomparably greater than that seen in ordinary obesity of a similar grade.

The psychic changes are varied, consisting chiefly of irritability alternating with depression. Failure of memory and apathy are often noted, and occasionally there is dementia. The mental symptoms while very common are less constant than the other cardinal signs.

Other symptoms suggestive of endocrin disturbance are the absence of sweating, and the increased appetite, especially for sweets. Abnormality

of the sugar metabolism is suggested by the low figure for blood sugar reported by Umber.

Vasomotor symptoms are very common. From time to time reddish or bluish transient swellings of the skin arise over the affected parts, and there is a marked tendency to hemorrhage from the nose, occasionally from the stomach and uterus. Bruising of the subcutaneous tissues on slight provocation is often noted.

Adiposis dolorosa is chiefly confined to the female sex, women being affected in the proportion of six to one, or more. The onset is usually at middle age, often at the menopause.

The etiology is obscure. A large proportion of the cases occur in neuropathic subjects, and insanity and epilepsy are often noted among the relatives. Alcoholism plays a part in some cases, probably more as an exciting factor than as a cause of the condition. Syphilis is emphasized by some authors, as in all obscure diseases, but there is no good evidence that it is of etiological importance, except in so far as it involves one of the endocrin glands.

The pathology strongly indicates that the condition arises from disease of the endocrin glands, which have been found more or less affected in almost every case. Thus Price states that the thyroid was found to be diseased in seven out of eight autopsies, being sometimes small and fibrous, sometimes enlarged and adenomatous, or the seat of calcareous deposits. The pituitary was markedly involved in fifty per cent, showing either tumor formation or inflammatory changes. Since then other cases have been reported showing well-marked hypopituitarism. Cushing in one case found the pituitary normal, but there was marked atrophy of the cerebral convolutions. The gonads are less frequently involved, showing atrophy and fibrosis.

The justification for ascribing adiposis dolorosa to disease of the endocrin glands is furnished not only by the symptomatology and the post-mortem lesions, but also by the marked improvement shown in some cases under thyroid therapy, and by the fact that the obesity is very resistant to dietetic treatment. Thus Umber describes a case following oöphorectomy, in which the weight remained stationary over a prolonged period on a diet containing only 900 calories.

The fact that numerous incomplete forms and border-line cases are met with by no means justifies, in the writer's opinion, the attempt to deny that adiposis dolorosa is a definite entity, or at least a polyglandular syndrome. In such cases it is to be expected that difficulty will be encountered in demonstrating endocrin disturbance, just as it is in "formes frustes" of myxedema and hyperthyroidism. There is no doubt that many cases have been reported as adiposis dolorosa which are instances of mistaken diagnosis, thus introducing more confusion into this difficult subject.

The prognosis is not good. The condition usually resists therapeutic

measures, and leads after a period of many years to death from cardiovascular disease or intercurrent infections, or occasionally from the effects of a pituitary tumor.

The Metabolism in Obesity

(1) **Exogenous Obesity.**—The basal metabolism has been found normal by all observers. This fact was first demonstrated by Rubner, who measured the gas exchange of a fat boy and his thin brother. The fat boy had a lower metabolism per kilo body weight but when reckoned according to surface area, there was no difference. Means, using the latest methods for reckoning surface area, has come to similar results. In a case of obesity with multiple nodular lipomata, recently studied by the writer, the basal metabolism was normal, and the lipomata were not affected by reduction of the body weight.

Grafe and Koch report some interesting observations, which show that overnutrition, if excessive, may actually increase the basal rate. Their first case was an emaciated man on whom a gastro-enterostomy had been performed for stenosis of the pylorus. When placed on a high calory diet (up to 98 calories per kilo) the gain in weight was much less than that expected. Metabolism experiments explained this deficiency. The basal rate, recalculated according to the Du Bois height-weight formula, rose from minus ten per cent to plus 27 per cent, and the total heat production increased 80 per cent, though the weight rose only 50 per cent. The increase in metabolism after taking food also rose from ten per cent of the caloric intake on a maintenance diet to 30 per cent on a high calory diet, the normal rise being about 14 per cent. Similar results were obtained in the case of an asthmatic boy of 14 years who displayed a voracious appetite. This boy showed a marked increase in the metabolic rate when placed on a diet of 100 calories per kilo, but failed to gain weight.

Similar results were obtained by Grafe and Graham(*a*) in overfeeding experiments on a dog.

The authors claim that heavy eaters usually have a higher metabolic rate than light ones, and suggest the possibility that in obesity this assumed normal response to overfeeding may be lacking.

Attempts have been made to demonstrate lowering of the metabolism in obesity by means of accurate estimations of the caloric value of the food over prolonged periods, but they are not absolutely conclusive, owing to the fact that retention of water may take place to a marked extent, thus masking the loss of fat. For example, Grafe in his third case found the weight constant for 22 days on a diet of 10 calories per kilo, 1000 calories in all; this would ordinarily lead to the conclusion that the metabolism was much lowered. Examination showed however that the basal metabolism was normal. The loss of body substance was masked by re-

tention of water. A similar retention of water has been found during milk-cures for obesity by Jacob and others.

The nitrogenous metabolism is normal, both as regards equilibrium and the nitrogen partition in the urine. During reduction cures nitrogenous equilibrium is maintained, provided that somewhat more than half of the maintenance calory requirement is given, as shown by von Noorden and Dapper. The deficit is made up by the combustion of the body fat, and protein is spared. If drastic measures are employed, such as the Moritz milk-cure (1500-1800 c.c. milk daily), marked loss of nitrogen takes place, up to 3 grams daily. This is in part due to the small nitrogen intake (6 gm.), in part to the low carbohydrate, so that the protein-sparing action of carbohydrate is lost.

Means found a low creatinin output, as reckoned per kilo body weight; this may be due simply to an increase of tissue which does not take part in the metabolism.

The blood shows occasionally an increased red count, fairly often a moderate anemia, but there is no evidence that the obesity is responsible for these changes. The blood lipoids have not been studied in obesity by modern methods.

The blood sugar was found increased by Roth in four out of sixteen fat patients, in the absence of glycosuria. It is possible that he was dealing with diabetics in the preglycosuric stage. Further studies on the sugar metabolism in obesity are desirable.

The restriction of fluids, so often practised in reduction cures, has little effect on the metabolism, tending rather to diminish it than to increase it; the loss of weight is due to loss of water and secondarily to the fact that less food is taken if the meal is dry.

The Metabolism in Endogenous Obesity. The chief interest centers in the basal metabolism. Up till recently no definite lowering of the basal rate in obesity had been found. During the last few years, however, such a condition has been reported, as will be noted in detail below. Where it was possible, the writer has recalculated the values, using the DuBois height-weight formula for surface area, and the table of Aub and DuBois for normal standards for age and sex. It should be noted that a normal variation of ten per cent in either direction is allowable.

Attempts have been made to show that simple obesity may be due to a lessening of the normal rise in the metabolic rate consequent upon the taking of food, but without success. Nor has it been possible to show that the obese accomplish work with an abnormally small expenditure of energy. It is possible that in the rare cases with lowering of the basal metabolism, such differences may be found to exist, but they have not been demonstrated up to the present.

The water balance is not infrequently abnormal in endogenous obesity, a fact that Grafe brings into relation with disturbance of the thyroid,

since he found in experiments carried out with Eckstein, that thyroidectomized animals gained very rapidly in weight, largely owing to the retention of water. This is in accord with previous work on the subject, which has shown that the loss of weight following thyroid administration is largely due to loss of water from the tissues. It is also possible that disturbances of the pituitary gland play a part in some cases, as is suggested by the abnormal water balance in diabetes insipidus and by the remarkable effect of posterior lobe extract in controlling the excessive diuresis of this condition.

(2) **Thyrogenous Obesity.**—In several cases a well-marked reduction of the basal metabolism has been noted. The most marked instance is Hausleiter's third case, a girl of thirteen years, with a reduction of 28 per cent. The case was complicated by swelling of the salivary glands, a syndrome to which attention has been directed above. No symptoms of myxedema were present. Grafe's first case, a girl 16 years old, showed a diminution of seventeen per cent, and presented a high grade of obesity, with some traits of myxedema, and is therefore not a pure case of obesity. It is of great interest as indicating the possibility of the combination of obesity and myxedema, both due to disturbance of function of the thyroid gland. McCaskey's sixth case, a girl 16 years old with hereditary syphilis, showed a reduction of 15 per cent, without any symptoms of myxedema. These are the only instances of thyrogenous obesity in the literature in which a definite reduction of the basal metabolism has been proven. There are other cases, however, in which the lack of response to extreme restriction of the diet renders a lowering of the metabolism probable. A good example is von Noorden's patient, a girl of 13 years, weighing 55 kg. On an accurately determined diet of 800 calories, with plenty of exercise, her weight remained constant. The continuous administration of thyroid extract, with a diet of 1500 calories, resulted in a cure of the obesity.

The effect of thyroid administration was very striking in Hausleiter's patient, resulting in an increase of basal metabolism of 33 per cent, the increase in the normal person varying from zero up to 15 per cent.

(3) **Hypophyseal Obesity.**—A definite reduction of the basal metabolism has been found in several cases, as may be seen in Table II. The values have been calculated by several methods so far as possible; the Harris-Benedict formulas do not apply to children and adolescents.

The figures in Means' cases have been recalculated according to the tables of Aub and DuBois, which had not been published when his article appeared. Two other cases studied by Means have not been included in the table because the diagnosis of hypopituitarism was regarded as only "probable." One of these, Mrs. L. L., showed a normal metabolism by present standards; the other, H. S., a diminution of eight per cent.

A study of the table shows that in three cases out of six there is a

TABLE II. BASAL METABOLISM IN HYPOPHYSEAL OBESITY

Author	*Case*	*Age*	Sex	*Metabolism DuBois Height-weight Per Cent*	*Metabolism DuBois Linear Per Cent*	*Metabolism Harris-Benedict Per Cent*
Grafe	IV	17	Male	—25	—	—
Means	N.K.	15	Male	—18	—18	—
Means	M.	28	Female	—12	—16	—9.6
Hausleiter	II	13	Male	— 8	—	—
Snell, Ford & Rowntree	VI	20	Female	+ 1.6	—	—
Snell, Ford & Rowntree	VII	24	Male	— 1.2	—	—

reduction of more than ten per cent, and in two, of more than 15 per cent. Since undernutrition can be excluded as a cause, it seems fair to conclude that hypophyseal obesity may be accompanied by a lowering of the basal rate.

The mode in which hypopituitarism reduces the metabolism is an interesting matter for speculation. The close interrelation of the pituitary and the thyroid renders the interpretation difficult. Thus Cushing found changes in the thyroid in all of his fifteen cases of pituitary insufficiency in which the gland could be examined, with excess of colloid and a low epithelium lining the acini. It is therefore possible that the lowered metabolism is due to secondary changes in the thyroid. Another possibility is that the normal pituitary secretion stimulates the thyroid gland to increased activity, and still another that it has a direct effect on the metabolism. The increased sugar tolerance found by Cushing in hypopituitarism, and the subnormal temperature are in favor of this view, especially as the contrary state, with elevation of the temperature and hyperglycemia, can be produced by injection of extract of the posterior lobe. Moreover, Cushing was able in some cases of hypopituitarism to produce a marked diminution of the obesity by feeding pituitary substance.

The effect of the administration of pituitary extract on the basal metabolism has not been sufficiently studied. In one of Means' cases, in which the diagnosis of hypopituitarism was considered probable, no effect was noted.

In addition to the increased sugar tolerance, which in some cases is so marked that 400 grams of levulose may be given without its appearing in the urine, a marked diminution of the blood sugar may occur, the very low value of 0.04 per cent being reported by Cushing.

Rosenbloom(*h*) in a study of a case of dystrophia adiposogenitalis, found the metabolism normal as regards sulphur, calcium, magnesium and phosphorus.

(4) **In Obesity of Genital Origin.**—The obesity which often, though by no means always, follows castration in both sexes, is attributed by most authorities to exogenous factors, such as change of temperament, leading to decreased muscular activity. The altered distribution of the fat, however, is sufficient justification for the assumption that an endogenous factor is at work, even if it is not responsible for the generalized adiposity.

The effect of castration on the basal metabolism has not been sufficiently studied from the experimental point of view. Loewy and Richter(*a*)(*b*), using the Zuntz-Geppert method, obtained some remarkable results. They found in a female dog a well-marked lowering of the basal rate, beginning ten weeks after operation, and persisting throughout the period of observation (six months). The reduction amounted to 20 per cent of the oxygen consumption per kilo, and to 12 per cent of the total oxygen consumption, although the dog gained ten per cent in weight during this period, so that an increased total consumption would have been expected. The administration of oöphorin (ovarian extract) caused a marked rise in the basal rate, up to 38 per cent above the normal previous to castration. Oöphorin had no such effect on a normal bitch.

In the case of a male dog, castration was followed by a similar but lesser diminution, amounting to 13.6 per cent of the oxygen consumption per kilo, the animal losing weight meanwhile. Testicular extract caused a slight rise in the metabolic rate, while singular to relate, oöphorin caused an increase of 44 per cent.

These remarkable results are much in need of confirmation. Lüthje, in a series of carefully conducted experiments, came to a contrary conclusion. A castrated male dog and the normal control from the same litter were put on the same accurately weighed diet, and confined in narrow cages to restrict muscular activity. In a period of six months, each dog gained in weight almost exactly the same amount. The castrate showed a rather *higher* total daily metabolism than the control as measured in the Pettenkofer apparatus. It should be noted, however, that the basal metabolism was not determined. In a similar experiment with female dogs, the spayed animal gained one kilo more than her sister before the operation, and this difference was maintained afterwards. The total CO_2 excretion per kilo per hour was almost identical in both animals. Loewy and Richter point out that the method followed by Lüthje was not adapted to show differences in the basal metabolism, since the gaseous exchange was measured over long periods, during which the taking of food and muscular activity would tend to obscure differences in the basal rate, and also that he failed to measure the metabolism before the operation. The whole question is therefore in need of further study.

In the case of man, there is as yet no good evidence that castration lowers the basal metabolism. In Grafe's third case, a woman of 44 years in whom the operation was performed for osteomalacia, and was followed

by obesity, the rate was plus 14 per cent. L. Zuntz(*a*)(*b*) has made a careful study of the gas exchange in three women before and after castration for pelvic inflammatory disease. Two showed a normal rate, and obesity ensued in one of them. In the third case, Zuntz concludes that a definite lowering of the basal metabolism was present 16 months after the operation, finding a diminution of the average oxygen consumption per kilo of 20 per cent. If, however, only the lowest values for the oxygen consumption are considered, the figures are the same both before and after, so that even in this case it is hardly permissible to speak of a lowering of the metabolism. In a case of oöphorectomy for osteomalacia, Zuntz claims to have found a lowering of the metabolism two years after operation, but since the patient lost 6 kilos in the meantime the very moderate reduction might well have been due to undernutrition. In a later publication he reports another case of castration for osteomalacia, with some lowering of the oxygen consumption per kilo afterwards, but since the absolute consumption was actually somewhat increased, and the patient gained weight meanwhile, the basal metabolism was probably not affected. Two female eunuchoids showed a normal gaseous exchange.

Zuntz administered oöphorin to all these patients, but was unable to detect any effect on the basal metabolism. The observations of Loewy and Richter therefore remain unconfirmed, at least so far as the *genus homo* is concerned.

It may therefore be concluded that obesity following castration is due, so far as our present knowledge goes, to the same causes as ordinary obesity.

The metabolism in obesity associated with disease of the pineal gland, and in adiposis dolorosa, has not been investigated.

The Treatment of Obesity

I. **The Treatment of Exogenous Obesity.**—Only the general principles of treatment fall within the scope of this discussion. For the details the reader may consult the excellent article by Locke(*b*) and the exhaustive monograph by von Noorden(*o*).

The two most important points are diet and exercise. The weight may be reduced by diet alone, but exercise is needed to maintain the tone of the muscles, and to facilitate the loss of weight by increasing the total combustion. A low fluid intake is neither necessary nor desirable, except in cases with cardiac decompensation. Massage is of benefit to weak patients, since it strengthens the muscles and thus facilitates the taking of exercise. The direct effect is very slight compared with active exercise, the oxygen consumption being increased by only ten per cent, or about as much as by moving the fingers.

In most cases it is best to reduce the weight very gradually, from five

to ten pounds a month being a suitable amount. This prolongs the period of dieting, which is of advantage in that it accustoms the patient to a small amount of food, so that he is not so likely to over-eat again after the weight has been sufficiently reduced. A slow reduction also avoids the danger of weakening the patient.

In the case of the extremely obese, and when cardiac decompensation complicates the picture, it is often advisable to go faster, so that from 20 to 30 lbs. are lost in the first month. In such cases it is well to begin with a marked reduction of the intake down to 1000 calories, and for this purpose a brief milk-cure, lasting not more than one or two weeks, is excellent. It is true that under these circumstances considerable body protein is burnt, but this does not appear to be harmful provided little exercise is taken, and the loss is quickly made up later after the diet is increased.

Since the greater part of the calories of the food is derived from fat and carbohydrates, these two forms of food will be the ones most restricted. In general it is better to cut the fats down to a low level and practise less restrictions of carbohydrates, since bulk with low caloric value can be supplied by the vegetables, and this satisfies the appetite, a very important matter if the treatment is to be long continued. In the case of persons who are very fond of fat, it may be advisable to allow more fat and less carbohydrate.

It is evident that weight may be reduced safely on a great variety of diets, provided that sufficient protein and carbohydrate are given to prevent loss of body protein. It is important that there should be enough variety to prevent the treatment from becoming irksome. A satisfactory diet will be found usually to contain a considerable amount of protein in the form of lean meat and fish, a moderate amount of carbohydrate, and little fat. Vegetables containing not more than ten per cent of carbohydrate usually may be allowed *ad libitum,* provided those containing more than this amount are excluded, while sugar is better cut down to a minimum, and breadstuffs limited to one or two slices daily. Fresh fruit may be taken in moderate amount.

Under such a régime the weight can be almost always satisfactorily reduced without calculating the calories or having the patient weigh the food. It is only necessary that the body weight be followed closely, with careful attention to the details of diet, including the quantity as well as the quality. For this purpose it is well to have the patient keep a daily list of the food taken at each meal. Occasional breaking over in the diet may be made up for by eating very lightly on the following day.

In difficult cases the caloric value of the food should be estimated. For this purpose Locke's(*a*) "Food Values" and Atwater and Bryant's tables may be consulted.

In the case of gouty patients the weight may be reduced safely on a

purin-free diet, but it is important that at least 50 grams of protein should be ingested, for otherwise there is danger of weakening the patient. This amount can be readily supplied in the form of milk, green peas and beans, with a limited amount of bread or cereal. Von Noorden, on the contrary, advises the use of meats during the reduction, preferring an attack of gout to the risk of cardiac weakness.

Nephritics without renal insufficiency and cases of essential hypertension may be reduced without limitation of protein. Cases with uremia on the other hand are seldom fat, and do not require reduction.

The use of thyroid extract in the treatment of simple obesity is seldom necessary, and should be restricted to cases that resist reduction on a greatly restricted diet. Such cases usually belong to the endogenous group, but the distinction is not always easy.

II. **The Treatment of Endogenous Obesity.**—Diet and exercise are important in this form also, but of themselves are not usually sufficient to effect a cure.

In the thyrogenous form, thyroid extract acts as a specific. It should be given in moderate doses, three to five grains a day, over periods of about eight weeks, with pauses of a week or two between. The effect of the drug should be watched, marked acceleration of the pulse or glycosuria indicating its withdrawal, or diminution of the dose.

The obesity of hypopituitarism is sometimes remarkably relieved by the administration of pituitary extract; in other cases no effect is observed. Thyroid extract is sometimes efficacious. Surgical treatment of the pituitary lesion usually does not relieve the obesity, for obvious reasons.

Obesity associated with syphilis of the thyroid or hypophysis may be favorably affected by antisyphilitic treatment.

The adiposity of dysgenitalism usually yields to dietetic measures, and glandular therapy does not often help here.

In adiposis dolorosa thyroid extract sometimes has a striking effect both as regards the obesity and the other symptoms. Often, however, it leaves one in the lurch, and then pituitary gland may be administered.

Acidosis . . . . . *Donald D. Van Slyke*

Historical—The Nature of Acidosis—The Normal Acid-Base Balance of the Body—The Normal Bicarbonate Concentration of the Blood, the Plasma, and Other Body Fluids—The Normal Hydrogen Ion Concentration of the Blood Plasma and Other Extracellular Fluids—The Mechanism Whereby the Normal Acid Base Balance is Maintained—The Neutralization of Acid by Buffers—Maximum Efficiency of Buffer Action—The Respiratory Regulation of the Free H_2CO_3 of the Blood—The Excretion of Acid by the Kidneys—The Formation of Ammonia—The Normal and Abnormal Variations in the Acid-Base Balance of the Blood, and the Resultant Effects on Physiological Functions—Relation of Changes in the Acid-Base Balance of the Blood to the Changes in the Other Body Fluids—Methods for Determining the State of Acid-Base Balance of the Body—Estimation of the Blood Bicarbonate and pH—The Alkali Retention Test for Alkali Deficit—Determination of the Alveolar CO_2 Tension—Determination of the Excretion Rate of Ammonia and Free Acid—Determination of Acetone Bodies in the Blood and Urine—Diagnosis and Therapy in the More Frequent Types of Acidosis—General Considerations Concerning Diagnosis—General Considerations Concerning Therapy—Acidosis in Certain Conditions—Diabetes—Nephritis—Diarrhea of Infants—Cyclic Vomiting of Children—Acidosis after Anesthesia.

Acidosis

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NEW YORK

Historical

The experimental foundation of our knowledge of acid intoxication was laid by Walter (1877) who fed rabbits varying amounts of hydrochloric and other acids by stomach tube and observed the effects. He found that "the CO_2 content of the blood is essentially proportional to its alkali content" and that it was reduced to an extent proportional to the amount of HCl administered. Ingestion of 1 gram of HCl per kilo reduced the CO_2 content of the blood from 27 volumes per cent to 2.5 and resulted in death. The most obvious physiological effects were rapid pulse and hyperpnea. About 15 minutes before death, breathing and pulse slackened, and the animals collapsed. Even at this stage they could be restored by intravenous injection of 0.5 gram of sodium bicarbonate. Dogs could not be killed by similar doses of acid, and Walter showed that their immunity was due to their power to form ammonia in amounts sufficient to neutralize the acid.

Stadelmann(*a*)(1883) made the clinical application of these observations. He noted that "the symptom complex of diabetic coma greatly resembles that of acid intoxication, as revealed by the work of Walter." Of these symptoms the "fearful terminal dyspnea" of diabetic coma vividly described by Kussmaul (1874) was most striking. It was also known, from work of Hallevoorden, that ammonia excretion is increased in diabetes. Stadelmann was led by these facts to look for proof of acid intoxication in diabetics, and discovered that large amounts of organic acid are excreted by patients in or near coma. He accordingly proposed bicarbonate administration as the logically indicated treatment.

The chief organic acid was identified, by work begun by Stadelmann and completed by Minkowski(*a*)(1884), as beta-hydroxybutyric acid.[1]

[1] Formation of beta-hydroxybutyric acid is always accompanied by formation of smaller amounts of acetoacetic acid, which represents one further step in oxidation.

$$\underset{\text{beta-hydroxybutyric}}{CH_3.CH(OH).CH_2.COOH} + O = \underset{\text{acetoacetic}}{CH_3.CO.CH_2.COOH}$$

Acetoacetic acid in solution spontaneously undergoes decomposition, gradual at body temperature, into acetone and carbon dioxid, so that acetone is always found

Magnus-Levy(*e*)(1899) completed the demonstration by showing that the chief source of the acid is incompletely burned fat, that in diabetic acidosis the rate of formation of beta-hydroxybutyric acid may exceed 100 grams per day (equivalent to 1 liter of N/1 acid), that the amounts found in the body at death are sufficient to cause fatal intoxication, and that even after the onset of coma death may sometimes be prevented by sodium bicarbonate administration. Magnus-Levy also emphasized the fact that, although most deaths in diabetic coma appear directly caused by acid intoxication, death may occur from other causes, and without premortal acid intoxication.

The terminal uremic coma of nephritis was pointed out by Kussmaul (1874) to be similar in its dyspnea to diabetic coma, and Jaksch(*f*)(1888) by means of a simple method for titrating the alkali content of the blood obtained results indicating the probable presence of acid intoxication, which has been confirmed with modern methods by Straub and Schlayer (1912) and Peabody(*c*)(*e*)(1914). The acidosis of nephritis differs notably from that of diabetes in the fact that the ketone acids, beta-hydroxybutyric and acetoacetic, do not occur in the former. Presumably the acidosis of nephritis is due to failure to excrete the acids produced by normal metabolism, rather than, as in diabetes, to abnormal acid production. Further investigations have indicated a rôle of acid intoxication in other conditions, some caused by the ketone acids (e. g., cyclic vomiting in children), others caused by unknown acids (ether narcosis and certain types of diarrhea in infants). Some of these conditions will be considered after a discussion of the nature of the changes caused by entrance of acids into the body at a rate exceeding that of their elimination.

The first unified exposition of the physiological and physico-chemical mechanisms by which the body maintains its normal acid-base balance was published by Lawrence J. Henderson(*a*)(1909) in a monograph which forms the basis of our present conceptions, and which, both in its viewpoint and in its details, may be accepted at present, with revision only to include additional facts that have been uncovered during the interim.

The Nature of Acidosis

Acidosis may be broadly defined as an abnormal condition caused by acid retention, that is, by the formation or absorption of acids at a rate exceeding that of their elimination. Such retention may be considered

when acetoacetic acid is present. These three substances are called the "acetone bodies," from the fact that the other two are readily converted into acetone, or "ketone bodies," from the fact that the acetone and diacetic acid are ketones. When in the blood or urine one of them is present it is apparently always accompanied by the other two; consequently a test for acetone or acetoacetic acid is a test for all three of the substances. Atypical comas also occur, due to collapse from causes other than acid intoxication, and differentiated from it by absence of air-hunger and of great ketonuria.

to have caused an abnormal state when it has either increased the hydrion concentration of the blood or lowered its alkali reserve below the extreme normal limit.

The results of acid retention, both clinically and on the physico-chemical state of the blood, are quite different according to whether the retained acid is carbonic or other than carbonic. Retention of carbonic acid causes increase in the hydrion concentration of the blood (or decrease in the pH).[2] It also raises the bicarbonate concentration by causing a shift to this form of some of the alkali which at normal pH is bound in other buffer salts.

Retention of acids other than carbonic, on the contrary, lowers the bicarbonate, a chemical equivalent of which is decomposed by the retained acid. Unless nearly all of the bicarbonate is thus decomposed, however, the pH is not changed from the normal, so long as there is no hindrance, mechanical or nervous, to the excretion of CO_2 by the lungs. The acidosis caused by retention of non-volatile acids, without fall in pH except as a terminal phenomenon, is the form commonly met in metabolic diseases, and until recently was the only form that had been observed clinically.

The bicarbonate is only one of a number of buffers in the blood, and in the body, exclusive of the blood, which are of importance in regulating the neutrality. The bicarbonate is the only important buffer, however, which can be used to neutralize acids without any change whatever in the blood pH. Furthermore the interreactions among the blood buffers are such that, as will be shown later, the bicarbonate, taken together with the pH, indicates the state of the entire system. We shall discuss below the

[2] The term pH was introduced by Soerensen (1912) as a convenient symbol for expressing minute hydrogen ion concentrations without resort to decimals, and for plotting changes over great ranges of hydrogen ion concentration. It is the negative logarithm of the hydrogen ion concentration, e.g., for $\frac{N}{100}$ hydrogen ion concentration, $C_{H^+} = 1 \times 10^{-2}$. The logarithm is therefore -2, the pH merely 2. The pH of water is approximately 7, i.e., the hydrogen ion concentration is 0.000,000,1 normal. The pH of solutions more acid than water is less than 7, that of solutions more alkaline is greater than 7, and each change of 1 in pH means a ten-fold change in hydrogen ion concentration, e.g., pH denotes ten-fold the hydrogen ion concentration of water, pH 5 denotes one hundred-fold. On the other side, pH 8 denotes 0.1, pH 9 denotes 0.01 the hydrogen ion concentration of water. For pH 7.35, that of blood, the hydrogen ion concentration is calculated as follows:—$7.35 = -8 + .65$, $0.65 = \log$ of 4.5 $\therefore$ Hydrogen ion concentration $= 4.5 \times 10^{-8}$.

The hydroxyl ion concentration at pH 7 is equal to that of the hydrogen ions, the dissociation constant of water being at ordinary temperatures approximately 10^{-14}.

$$C_{H^+} \times C_{OH'} = 10^{-14}.$$

Consequently the log of the OH′ concentration is calculated from the pH by subtracting 14 from the pH, e.g., pH $= 12$; log OH′ concentration $= 12 - 14 = -2$. OH′ concentration $= 0.01$ N.

$=$

It follows that any OH′ concentration may be expressed in terms of H^+ concentration or vice versa, values in terms of pH affording a convenient means of covering the entire field of reaction, both acid and alkaline.

normal and abnormal variations of the blood pH and bicarbonate values and the changes in the acid-base balance of the body indicated by changes in these values.

The Normal Acid-Base Balance of the Body

1. The Normal Bicarbonate Concentration of the Blood, the Plasma, and Other Body Fluids.—At the pH and CO_2 tension existing in the blood all alkali in excess of that bound by the non-volatile acids is converted into bicarbonate. None can exist as free alkali (NaOH), and only a negligible fraction of a per cent as normal carbonate (Na_2CO_3). From the equation $\frac{CO''_3}{HCO'_3} = \frac{4.27 \times 10^{-11}}{H^+}$ (Seyler and Lloyd, 1917) one calculates that at blood reaction, $H^+ = 4 \times 10^{-8}$, the ratio

$$\frac{CO''_3}{HCO'_3}, \text{ or } \frac{Na_2CO_3}{NaHCO_3}, \text{ is } \frac{1.}{1000}$$

Therefore, 99.9 per cent of the alkali in the blood not bound by acids other than carbonic is in the form of bicarbonate.

The concentration of the bicarbonate in the whole blood is usually from 0.02 to 0.027 $\underline{\underline{M}}$, corresponding to 45 to 60 c.c. of CO_2 bound as bicarbonate in 100 c.c. of blood. In the plasma it is appreciably higher, 0.022 to 0.031 $\underline{\underline{M}}$, or 50 to 70 volumes per cent of bicarbonate CO_2 (Van Slyke and Cullen, 1917). It follows that in the red cells the bicarbonate concentration must be still lower than in the whole blood, and it is found to be only one-half to two-thirds as great as in the plasma (Joffe and Poulton, 1920).

In the body fluids other than blood such information as we have indicates that the bicarbonate concentration approximates that in blood plasma. We have observed bicarbonate values normal for blood plasma in ascitic fluid and pleural exudates, and Parsons and Shearer (1920) have observed in the cerebrospinal fluid both bicarbonate and pH values normal for blood plasma. Collip and Backus(*a*)(*b*)(1920) observed that the bicarbonate of the spinal fluid followed that of the blood plasma when the latter was altered, although the changes in the fluid might lag some hours behind those in the plasma. Palmer and Van Slyke (1918) found that absorbed bicarbonate is not retained in the blood, but is distributed to the body fluids in general with approximate uniformity.

2. The Normal Hydrogen Ion Concentration of the Blood Plasma and Other Extracellular Fluids.—The average normal hydrogen ion concentration of the blood plasma lies at or near the slightly alkaline point $H^+ = 4 \times 10^{-8}$, or pH = 7.4. This fact was demonstrated on the basis

of material then available by L. J. Henderson in 1909, and has been confirmed by Lundsgaard(*a*) (1912) and other subsequent investigators, utilizing the gas chain method. Parsons (1917) working with especial precautions showed that the actual pH value determined is that of the plasma, and that the pH of venous blood in a given individual is normally only 0.02 below that of arterial blood. The maximum normal range of variation of blood reaction in different individuals appears to be indicated by pH 7.3 to 7.5. It is possible that when errors of technique are more completely excluded this range will become still narrower.

Under extreme abnormal conditions the pH may fall as low as 6.95, but at or above this point it is probable that coma occurs, and, from the fact that lower pH values have not been observed, it is doubtful that further decrease is compatible with life.

This was the lowest point observed by Hasselbalch and Lundsgaard(*b*) (1912) in rabbits killed by prolonged breathing of air with contained CO_2. It is also the lowest point observed by Van Slyke, Austin, and Cullen (1920) in experiments on etherized dogs. A pH of 6.95 was in one instance determined electrometrically by Cullen (unpublished) in the blood of a nephritic man in coma a few hours before death.

By voluntary deep breathing, on the other hand, carbonic acid may be blown off until the blood alkalinity rises to a pH of 7.7 or 7.8 (Davies, Haldane, and Kennaway, 1920; Collip and Backus, 1920), at which point, however, symptoms of tetany appear (Grant and Goldman, 1920). It therefore appears that the extreme range of reaction compatible with life lies approximately between pH 6.95 and pH 7.80 and that the normal range is within limits no greater than pH 7.3 to 7.5, and possibly somewhat narrower.

Concerning the pH of the body fluids other than blood plasma our knowledge is limited, but such as it is indicates that these fluids approximate the blood plasma closely in their reaction. (By body fluids are meant the fluids within the body proper, such as lymph, cerebrospinal fluid, transudates, exudates, but not secretions such as gastric juice or urine). Parsons and Shearer (1920) found in the cerebrospinal fluid a pH normal for blood plasma.

In the body fluids, data, to which we refer above, have shown that the bicarbonate is normal for blood plasma. As there is reason to believe that the CO_2 tension in these fluids approximates that of the arterial blood (Haggard and Henderson, 1919) it is probable that a bicarbonate concentration normal for blood plasma indicates also a $\frac{BHCO_3}{H_2CO_3}$ ratio, and therefore, as will be shown presently, a pH, normal for blood plasma.

The Mechanisms Whereby the Normal Acid-Base Balance Is Maintained

The mechanisms by which the acid-base balance of the body in general, and of the blood plasma in particular, is maintained may be divided into two groups, those which retard change in the blood pH as a result of the normal gain and loss of CO_2 during the cycle of the gas exchange, and those which retard pH change when non-volatile acids enter the blood, or when abnormally great CO_2 retention occurs. The mechanism that cares for the normal changes of the gas cycle has been recently discussed in detail elsewhere (Van Slyke(*i*), 1921). It is the mechanism directed against non-volatile acids, and abnormally retained CO_2, which is of interest in acidosis, and which we shall consequently discuss here.

The order in which the components of this mechanism respond to acid invasion may be outlined as follows:

1. The *buffers* of the blood, seconded more or less promptly by those of other parts of the body, partially neutralize the acid the instant it enters the blood. The neutralization is described as partial, because the buffers unaided do not completely prevent reaction change, although they may reduce it to insignificance. This first defense is purely chemical, as distinguished from the three following, which are at least partly functional.

2. The *lungs accelerate the rate of CO_2 excretion,* and thereby reduce the H_2CO_3 of the blood until a normal $H_2CO_3 : BHCO_3$ ratio is restored, and therefore a normal pH. When this has been accomplished the $BHCO_3$ (total bicarbonate, B representing Na + K + other bases) is still low, if the invading acid is other than carbonic, but all the other buffers have regained their normal supplies of alkali. The bicarbonate alone registers by its fall the amount of buffer alkali neutralized by the retained acid. The condition is now one of "compensated alkali deficit"; the buffer alkali is reduced, but compensating reduction of free H_2CO_3 has restored a normal pH.

3. Finally *the kidneys excrete acid products,* and

4. *The organism forms ammonia,* which is also excreted.

By (3) and (4) the invading acid is removed, and replaced by bicarbonate until the $BHCO_3$ has been restored to its normal concentration. The acid-base balance of the blood is now again normal, both in pH and in buffer alkali.

If the rate of elimination of acid by excretion and ammonia formation together fails to equal the rate of acid formation, however, then, instead of returning from compensated alkali deficit to normality, the condition passes to one of terminal uncompensated acidosis. The bicarbonate is reduced to a small fraction of normal, and in addition the available alkali of the hemoglobin and other buffers is drawn upon. When by these

drafts upon their alkali the buffer salts have been so far reduced, and the free buffer acids so far increased, that an unendurably low pH results, death from acid intoxication follows.

We shall now discuss in some detail the above four parts of the mechanism whereby the body minimizes reaction changes resulting from acid invasion, and restores its acid-base balance to normality after such disturbances have occurred.

1. The Neutralization of Acid by Buffers.—The buffers are the direct defenders of neutrality by which invading acids are first met, and they are also involved in the subsequent restoration of normal reaction by respiratory regulation of the CO_2 tension, and by renal excretion of other acids. Their position in neutrality regulation is so central that unless their mode of action is clearly seen the whole combined physiological and chemical mechanism for neutrality maintenance escapes one's grasp. We shall therefore discuss the buffers, both as to their general nature and their specific behavior in the blood.

a. *The Nature of Buffers.*—Buffers are salts of either weak bases or weak acids, and are characterized by their ability to enable solutions in which they are present to receive additions of limited amounts of either acid or alkali with much less change of pH than would be caused by the same additions to water, or to a solution containing only salts, such as NaCl, that have no buffer power. All the important buffers of the blood, viz., the bicarbonates, phosphates, and the alkali salts of the proteins, are salts of weak acids. Of each buffer, part is present as free acid, part as the salt of a strong base, and the pH of the blood is determined by the relative proportions of buffer salts and free buffer acids respectively.

The alkali salts which constitute the buffers of the blood are in effect reservoirs of alkali, a portion of which they give up to neutralize carbonic or any other acid that enters the blood. In this manner act the phosphates, and also the alkali salts of the plasma proteins and of the hemoglobin.

In regard to such buffers two general laws may be stated, the principles underlying both of which may be found in L. J. Henderson's(*a*) monograph on the regulation of body neutrality (1909).

1. The hydrogen ion concentration of the buffer solution is proportional to the ratio $\frac{\text{free acid}}{\text{free salt}}$ or $\frac{HA}{BA}$. Examples of such ratios in the blood are $\frac{H_2CO_3}{BHCO_3}$, $\frac{BH_2PO_4}{B_2HPO_4}$, $\frac{HHbO_2}{BHbO_2}$, $\frac{HHb.}{BHb}$ (B is used to indicate any monovalent base, such as Na or K, A to indicate the acid radical, $BHbO_2$ the alkali salt of oxyhemoglobin, $HHbO_2$ the free oxyhemoglobin, BHb and HHb the salt of reduced hemoglobin and the free protein respectively.)

2. A given buffer is most efficient in maintaining constancy of pH (that is, in minimizing the *proportion* by which H^+ is changed by a given addition of acid or alkali) when the ratio $\frac{HA}{HB}$ approximates 1, and H^+ equals K, the dissociation constant of the free acid forming one of the buffer pair.

The theoretical demonstration of these two laws is the following:

1. *Relationship between pH and the ratio* $\frac{HA}{BA}$ (or $\frac{\textit{free buffer acid}}{\textit{buffer salt}}$).

This relationship is derived as follows:

Since the reaction of electrolytic dissociation of an acid into H^+ and anion is $HA = H^+ + A'$, it follows from the law of mass action that, at equilibrium,

$$1)\quad K \times HA = H^+ + A',$$

K being the dissociation constant of the acid. Hence

$$2)\quad H^+ = K \times \frac{HA}{A'}$$

But when the buffer mixture is the salt of a very weak acid plus some free acid, only an infinitesimal part of the anion, A′, originates from dissociation of the free acid (H_2CO_3 in the concentration present in the blood, for example, is dissociated into H^+ and HCO_3' only to the extent of about 1/10,000). Essentially all of the anion originates from dissociation of the salt, BA, into B^+ and A′. Most salts in 0.1 to 0.01 molecular concentration undergo such dissociation to the extent of 60 to 90 per cent of the amount present. If the degree of dissociation be represented by λ, the concentration of anions is $A' = \lambda BA$, and Equation 2 may be written

$$3)\quad H^+ = K\frac{HA}{\lambda BA}.$$

Since λ varies to a relatively slight extent over ranges of concentration within such limits as are found in blood constituents, one may state as a close approximation that $\frac{K}{\lambda} = K_1$ and

$$4)\quad H^+ = K_1\frac{HA}{BA}.$$

In terms of pH, since $pH = -\log H^+$, Equation 4 is

$$5)\quad pH = -\log K_1 - \log\frac{HA}{BA}, \text{ or}$$

$$6)\quad pH = pK_1 + \log\frac{BA}{HA}.$$

The form represented in Equation 6 was first introduced by Hasselbalch (*b*) (1916).

Expressing $-\log K_1$ as pK_1 the value of pK_1 for $B_2HPO_4 : BH_2PO_4$ mixtures was shown by Sœrensen (1909) and by Clark and Lubs (1916) to be approximately 6.8. For $BHCO_3 : H_2CO_3$ solution in the concentrations normally found in blood plasma Hasselbalch (1916) found pK_1 at body temperature to have a value of 6.1. His results indicated in fact that by determination of the ratio $BHCO_3 : H_2CO_3$ the pH of a blood sample could be estimated with Equation 6 as accurately as by the standard electrometric method.

The figure for pK_1 actually given by Hasselbalch is 6.4, because he used the equivalent concentration of H_2CO_3, which is twice the molecular, in calculating the $\frac{BHCO_3}{H_2CO_3}$ ration. When used with the molecular ratio adopted by L. J. Henderson and, so far as we have observed, all other authors except Hasselbalch, the value of pK_1 must, therefore, be reduced by log 2, or 0.3, giving pK_1 the value 6.1.

2. Maximum Efficiency of Buffer Action When $\frac{BA}{HA} = 1$, $H^+ = \frac{K}{\lambda}$ and $pH = pK_1$.—The identity of these three expressions is shown as follows: If in Equation 3 above, $\frac{HA}{BA}$ is replaced by 1, the equation becomes $H^+ = \frac{K}{\lambda}$. Similarly if in Equation 6, $\frac{BA}{HA}$ is replaced by 1, $\log \frac{BA}{HA}$ becomes O, and the equation becomes $pH = pK_1$.

The fact that a buffer mixture of a weak acid and its salt has its maximum efficiency, when $\frac{BA}{HA} = 1$, in diminishing changes in reaction caused by adding either base or acid, has its basis in the general proposition, that in the ratio $\frac{a}{1-a}$ a given change in a produces the least percentage change in the ratio when $a = 0.5$ and the ratio is consequently unity. The relationship is exemplified graphically by a curve expressing as ordinates values of the ratio $\frac{BA}{HA}$, as abscissæ values of pH. For bicarbonate at approximately normal blood plasma (0.03 *M*) concentration, the curve indicated by figure 1 is obtained. The curve is calculated from the approximate equation $pH = 6.1 + \log \frac{BHCO_3}{H_2CO_3}$, the, for the present purposes, insignificant variations in pK_1 from the value 6.1 being neglected. It is evident from inspection that the curve is

steepest in the middle, when H_2CO_3 and $BHCO_3$ are equal (50 per cent of the CO_2 as $BHCO_3$). This fact means that at this point the addition of sufficient acid or alkali to change a given amount of the total CO_2 from $BHCO_3$ to H_2CO_3, or vice versa, causes less shift in pH than at points near either end of the curve, where the ratio $BHCO_3 : H_2CO_3$ is much greater or smaller than 1. For example, changing the per cent of CO_2 as $BHCO_3$ from 50 to 60 alters the pH from 6.10 to 6.26, a change of 0.16;

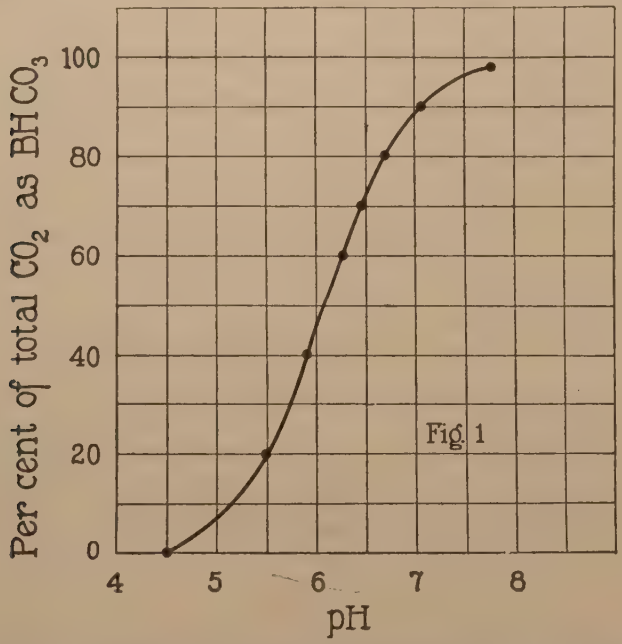

Fig. 1. Action of $NaHCO_3:H_2CO_3$ buffer, showing maximum buffer effect at middle of curve when $NaHCO_3:H_2CO_3$ ratio = 1.

while changing the percentage from 85 to 95 raises the pH from 6.85 to 7.40, a change of 0.55. It is evident that at pH 7.40, the reaction of normal blood plasma, when the ratio $\frac{BHCO_3}{H_2CO_3} = \frac{20}{1}$, bicarbonate as a buffer is acting at far from its most efficient point.

The phosphates are more efficient at blood pH. When the ratio $\frac{B_2HPO_4}{BH_2PO_4} = 1$, the pH is 6.8, much nearer to the reaction of normal blood than the 6.1 pH of the $BHCO_3 : H_2CO_3$ pair when their ratio is unity. The phosphates are present in so small an amount in plasma that they play a quantitatively negligible rôle, but they are more important in the cells. Of all the organic and inorganic acids, other than proteins, that might conceivably be used as buffers by the organisms, L. J. Hender-

son (1909) estimates that carbonic and phosphoric most nearly approximate maximum efficiency at the blood reaction, despite the fact that the blood pH is not very near the point of maximum efficiency of either buffer. It is of importance, however, that this point is in both buffers at a lower pH than that normal for blood, so that if the blood pH falls, the phosphate and carbonate buffers oppose the change with an efficiency which increases as the change approaches the danger point. At pH 6.95, which appears to be the most acid point consistent with life in man, the phosphates have very nearly their maximum buffer efficiency.

While the organism has appropriated the best available, although not ideal, buffers that the external laboratories of nature offer, it appears to have manufactured, in the chief blood proteins, buffers of its own which are nearly ideal.

b. The Interchange of Buffer Effects Between Blood Cells and Plasma. —It remains to add an account of the peculiar manner in which buffer effects are interchanged between cells and plasma. The cells are much richer in the buffers effective at blood pH than is the plasma, but by means of interchanging HCl and H_2CO_3 are able to extend their buffer effect to the plasma, even though the buffers themselves (hemoglobin and phosphate) do not leave the cells.

Below is a diagram which although from lack of available data it is necessarily incomplete, nevertheless appears to represent the chief buffer factors that maintain the constancy of the blood pH, and to indicate the anion exchange that makes the cell buffers available to the plasma. The equilibria as written are all shifted from left to right by increase in H_2CO_3.

PLASMA	CELL WALL	CELL
(1) $H_2CO_3 + NaCl \rightleftarrows NaHCO_3 + HCl$	$\rightarrow HCl \rightarrow$	(3) $HCl + K_2HPO_4 \rightleftarrows KH_2PO_4 + KCl$
(2) $H_2CO_3 + Na\ Protein \rightleftarrows NaHCO_3 + H\ Protein$		(4) $HCl + KHbO \rightleftarrows HHbO + KCl$
		(5) $HCl + KHb \rightleftarrows HHb + KCl$
	$\rightarrow H_2CO_3 \rightarrow$	(6) $H_2CO_3 + K_2HPO_4 \rightleftarrows KH_2PO_4 + KHCO_3$
		(7) $H_2CO_3 + KHbO \rightleftarrows HHbO + KHCO_3$
		(8) $H_2CO_3 + KHb \rightleftarrows HHb + KHCO_3$

"Na Protein" is used to indicate the total alkali salts of the plasma proteins, "H Protein" the free proteins not combined with base. Similarly "KHbO" and "HHbO" are used to indicate the alkali salt of oxyhemoglobin and the oxyhemoglobin not combined with alkali, respectively. "KHb" and "HHb" are used similarly for reduced hemoglobin. In the plasma the base is indicated as Na, in the cells as K, to indicate the fact

that, in human blood at least, these two bases predominate in the two locations, and do not diffuse freely from one to the other. There is, of course, some K in the plasma, and some Na in the cells, which the above diagram fails to show.

The cell buffers, phosphates and alkali salts of hemoglobin, from their location in the cell are able, when the plasma pH falls, to draw HCl from the plasma into the cells, where it is neutralized by Reactions 3, 4, and 5. This withdrawal permits the increase of plasma $BHCO_3$ by Reaction 1. The cells are also freely permeable to H_2CO_3, so that the latter can enter them and be neutralized by Reactions 6, 7, and 8. The cells can therefore, if acid enters the plasma, use their buffers both to increase the $BHCO_3$ and lower the H_2CO_3 in the plasma, and thereby lessen the fall in plasma pH.

Concerning the relative parts which the different reactions in the diagram play, our knowledge is not exact. It appears, however, that a given change in H_2CO_3 causes the same change in $BHCO_3$ in the cells that it does in the plasma. That is, the $BHCO_3$ formed by Reactions 1 and 2 in the plasma equals that formed by Reactions 6, 7, and 8 in the cells. This is exemplified by the data of Van Slyke and Cullen (1917) and Joffe and Poulton (1920).

Furthermore it is known that from 50 to 75 per cent of the $BHCO_3$ formed in the plasma by a given increase in H_2CO_3 results from Reaction 1 and the accompanying shift of HCl into the cells.

A result of the latter fact is that the $BHCO_3$ of separated plasma is dependent on the H_2CO_3 concentration of the whole blood at the moment the plasma is separated. Consequently, if the blood is allowed to lose or absorb CO_2 after it has left the body and before the plasma is separated from the cells, gross changes occur in the plasma bicarbonate, so that the latter ceases to represent at all the conditions of the blood when it was drawn. For example, if freshly drawn blood is poured back and forth from one tube to another for a few minutes, half the total CO_2 may be lost and all the reactions represented in the diagram move from right to left, with the result that the plasma when subsequently separated may have only about half as much $BHCO_3$ as when it was drawn from the body. Subsequent restoration of the original H_2CO_3 to the separated plasma restores only about ¼ of the $BHCO_3$, since because of absence of the cells Reaction 1 can no longer to reversed, and only the small amount of $BHCO_3$ formed by reversing Reaction 2 can be restored. For studies of the acid-base balance on the plasma, the latter must be separated before there has been any escape of CO_2 from the whole blood.

c. The Interchange of Buffer Effects Between the Blood and the Tissues.—The buffers of the tissues are, like those of the blood cells, and probably by a similar exchange mechanism, available to assist in maintaining neutrality of the blood plasma. The tissue buffers thus multiply several

fold the amount of acid that the blood can receive without fatal fall in pH.

The fact that the buffers of the cells and fluids outside of the blood assist the blood in maintaining its acid-base balance was shown by Van Slyke and Cullen (1917). They injected into the veins of a dog more than enough dilute sulphuric acid to neutralize all the blood buffers, and found that about five-sixths of the acid had been neutralized by alkali from other sources, as the decrease in blood bicarbonate was equivalent to only about one-sixth of the injected acid. It therefore appears that disturbances in the acid-base balance of the blood are, at least when of considerable magnitude, transmitted to the rest of the body, the buffers of which assist those of the blood in maintaining its neutrality.

d. The Physiologically Available Alkali of the Bicarbonate and of the Other Blood Buffers.—Definition of Alkali Reserve.—In order that a buffer shall neutralize an acid (HCl for example) *without change in pH* it is necessary that the buffer acid HA, set free by the reaction $BA + HCl = BCl + HA$, shall be completely removed, and in addition as much of the HA formerly present as may be necessary to keep the ratio BA : HA at the original value. Of the blood's important buffers, plasma protein, cell phosphates, hemoglobin, and bicarbonate, only the bicarbonate has an acid (CO_2) which can be quickly removed. Under all circumstances, physiological and pathological, in which the respiratory apparatus is not specifically affected, it appears that the CO_2 is so regulated that a normal pH is maintained. This is accomplished even by the ill diabetic or nephritic so efficiently that, until the $BHCO_3$ has been reduced by invading acids to $\frac{1}{4}$, and perhaps even $\frac{1}{8}$ of its normal value, the H_2CO_3 is reduced in the same proportion, and a normal pH is maintained.

So long as the pH is kept constant in the above manner, all the changes in buffer alkali are those of the bicarbonate. For at a constant pH the ratio BA : HA remains constant for each buffer, and however much depletion the $BHCO_3$ may suffer, the alkali salts of the other buffers are quite unaffected (that this is true has been demonstrated experimentally as well as theoretically).

One liter of average human blood contains bicarbonate sufficient to neutralize 0.022 equivalent of acid, or 22 c.c. of N/1 acid, and this is the maximum that it could neutralize without change in pH, even if the CO_2 tension were reduced to zero.

However, at the cost of a fall in pH, the alkali of the other buffers can be drawn upon, and since the publication of Van Slyke and Cullen's paper conditions have been observed (certain cardiac cases, Peters and Barr(*b*), 1921; ether anesthesia, Van Slyke, Austin and Cullen, 1920) in which the pH does fall below normal. From data already quoted it appears that for a short time at least the pH may fall as low as 6.95, although not lower, without fatal results.

The maximum available alkali of the blood is therefore the alkali of the bicarbonate plus that portion of the other buffer alkali which is yielded when the pH changes from normal to the minimum compatible with life. The amount of such buffer alkali may be estimated by increasing the CO_2 tension of the blood until the pH is reduced to 6.95. All the alkali given up by the other buffers is bound by the H_2CO_3 and thereby turned into bicarbonate under these conditions, so that the increase in bicarbonate above that at normal CO_2 tension represents the available alkali of the other buffers. By extrapolation in Fig. 3 of the average normal CO_2 absorption curve of human blood computed by Peter and Barr (*a*) (1921) we find that this available alkali from buffers other than bicarbonate is about 0.01 $\underline{\underline{M}}$ in concentration, or approximately half the normal bicarbonate alkali.

The average total available alkali of normal human blood may therefore be summarized as

0.022 $\underline{\underline{M}}$ bicarbonate alkali, equivalent to 49 volume per cent of bicarbonate CO_2, of which ¾ to ⅞ may be used for neutralization of acid without change in pH.

0.010 $\underline{\underline{M}}$ alkali from other buffers, available only when the pH falls to 6.95.

Total 0.032 $\underline{\underline{M}}$ alkali available with maximum fall in pH compatible with life.

Of the 0.010 $\underline{\underline{M}}$ alkali from buffers other than bicarbonate the greater part is normally bound by hemoglobin (Van Slyke, 1921, p. 160).

In a broad sense, therefore, the alkali reserve of the blood includes not only the bicarbonate, but in addition about half as much more alkali of the other blood buffers. In a still broader sense one might add the tissue alkali considered below, since during acid invasion it becomes available to assist in maintaining the blood neutrality.

In the interest of clearness and convenience, however, we shall use the term *alkali reserve* to indicate *the blood bicarbonate measured at such CO_2 tension that the pH is physiologically normal.* This usage seems desirable for the reasons that the bicarbonate as defined is a quantitatively measurable value, and that it represents the only alkali in the blood that can be used to neutralize acid without change in pH. Furthermore "blood bicarbonate" and "alkali reserve" have for some time been used synonymously in the literature, and the above definition does not change, but merely defines more accurately, the recognized conception of the alkali reserve.

2. The Respiratory Regulation of the Free H_2CO_3 of the Blood.—Almost as rapid as the neutralization by the buffers is the compensation

of non-volatile acid invasion by respiratory reduction of the free carbonic acid. Whenever, either by increased rate of CO_2 production or by decomposition of $BHCO_3$ by acid, the ratio $BHCO_3 : H_2CO_3$ ratio is decreased, the respiration is accelerated. More rapid ventilation follows until the H_2CO_3 of the blood is so reduced that the normal pH is restored. The respiratory response is so sensitive that Campbell, Douglas, Haldane, and Hobson (1913) observed that an increase of only 1 mm. in CO_2 tension, sufficient to change the blood pH by less than 0.01, accelerated the minute volume of air breathed by 60 per cent.

When retention of non-volatile acids occurs gradually, as in metabolic disease, the respiratory compensation rather than the buffers is the first observable defensive reaction of the body. The respiratory control, unless deadened by narcotics or toxins, is so sensitive that the slightest fall in pH causes a compensatory increase in respiration and restoration of a normal pH. The usually observed occurrence in naturally occurring acid retentions is therefore a gradual lowering of the blood bicarbonate, with proportionately increasing minute volume of the respired air, the blood pH remaining normal until the bicarbonate has fallen to ¼ or even ⅛ of the normal level. Only when the fall is so great the respiration can no longer increase in proportion to it does the pH begin to drop, indicating that the buffers other than bicarbonate are being called on as the next defense to the body's neutrality.

3. The Excretion of Acid by the Kidneys.—When either the pH or the alkali reserve of the blood has been lowered the normal response of the kidneys is to excrete acid products at an increased rate and restore the internal condition to normal. This is true even when the acids concerned are so strong that they can not themselves be excreted as free acids in any significant proportion. Such acids react in the body with excretable buffers, chiefly the phosphates, by such reactions as $B(BHPO_4) + HCl = H(BHPO_4) + BCl$. The acid phosphate $H(BHPO_4)$ formed by the reaction is excreted as such in the urine, while the strong acid is excreted as the salt (e.g., BCl) formed by the reaction with the buffer (Fitz, Alsberg, and Henderson, 1907).

The pH of the urine varies from 4.8 to 7.4 (Henderson and Palmer, 1912). Whenever, as is almost always the case, the urinary pH is below 7.4, the kidneys excrete products the retention of which in the blood would tend to lower its pH below that point. Such acid products, so far as quantitatively significant amounts are concerned, are necessarily buffers. Strong acids, like HCl, can be present free in only infinitesimal amounts even at the lowest urinary pH. Of the acid products excreted, the chief is normally acid phosphate. In the blood, at pH 7.4, the ratio $\frac{B(BHPO_4)}{H(BHPO_4)}$ is 3.93, 80 per cent of the total buffer being in the form of the alkaline

salt, 20 per cent as the acid salt. Consequently whatever phosphate above 20 per cent of the total is excreted as BH_2PO_4 represents acid removed from the body. At pH 4.8 99 per cent is in the form of the acid salt. It is therefore possible for a gram molecule of excreted phosphate to represent a maximum of 0.79 gram equivalents of acid removed from the body.

β-hydroxybutyric acid, of which the acid dissociation constant is 2×10^{-5} (Henderson and Spiro, 1909) is excreted at pH 4.8 to the extent of 55 per cent as the free acid, whereas in the blood it is practically 100 per cent in the form of alkali salt. Therefore it is possible for a gram molecule of excreted beta-hydroxybutyric acid to represent 0.55 gram equivalents of acid removed from the body.

The most logical measure of the amount of excreted acid is the amount which is determined by titrating the urine with alkali from its observed pH to pH 7.4 (Henderson and Palmer, 1914). The amount usually thus excreted by an adult is 200-400 c.c. of N/10 acid per 24 hours. Acid excretion appears to increase when a fall occurs in either blood pH or alkali reserve. When the blood pH is reduced, the acid excretion increases, even though the fall in pH be due to CO_2 excess, and without reduction in the total buffer alkali of the blood (Davies, Haldane, and Kennaway, 1920). Also, however, when the blood pH is normal, but the $BHCO_3$ has been lowered, as in compensated diabetic acidosis, the acid excretion is increased in the apparent attempt to raise the alkali reserve back to its normal level. The excretion of free acid may in such cases rise to as high as 1,000 c.c. of decinormal acid per twenty-four hours.

4. The Formation of Ammonia.—Even more important, in man, for restoring the available alkali of the body than the excretion of free acid is the formation of ammonia. The proportion of urinary nitrogen excreted as ammonia is normally about 5 per cent, and the amount 300 to 500 c.c. of 0.1 N NH_3 per 24 hours. In severe diabetic acidosis it may be 10-fold as great.

Ammonia formation rises, like acid excretion, in response to a fall in either blood pH or alkali reserve. It appears to be fairly proportional to the amount of acid metabolites formed, exclusive of acid phosphate. This is peculiar among the acid products in that it is excreted almost entirely as free acid, $H(BHPO_4)$, and does not stimulate ammonia formation (Marriott and Howland, 1916). The highest ammonia excretions clinically observed have been seen in diabetic ketonuria, where the excretion may reach 5,000 c.c. of N/10 NH_3 per day. It can, therefore, rise to a height several times greater than the excretion of free acid.

The sum, ammonia plus titratable acid, bears a sufficiently close relation to the blood bicarbonate to be used as a rough measure of the latter

in diabetes (Van Slyke and Fitz(*a*), 1917), and is related to it as indicated in Table II on p. 85.

The Normal and Abnormal Variations in the Acid-Base Balance of the Blood, and the Resultant Effects on Physiological Functions

When the above outlined defenses against acidification fail to respond normally, or when the acid invasion is too rapid to be met, or when the centers regulating the physiological portions of the mechanism become either over- or undersensitive, the acid-base balance is deranged. In order to recognize the characteristics of the blood conditions that result, it is desirable to consider the variations that lead to or involve both alkalinization and acidification, since conditions occur under which abnormality in either direction may be mistaken for its opposite unless data are available to furnish a consideration of all the possibilities.

The possible variations in the acid-base balance of the blood may be stated as follows: the blood bicarbonate may be high, low, or normal, and in each of these conditions the pH may be high, low, or normal. There are thus nine theoretically possible conditions. Only one of them is normal, that in which both bicarbonate and pH are within the normal limits. At the time of Van Slyke and Cullen's original paper (1917) only two of the abnormal possibilities had come under clinical observation, that in which bicarbonate is low, and pH normal (compensated acidosis), and that in which bicarbonate is very low, and pH also low (uncompensated acidosis). Now, however, as the result of the recent work of Y. Henderson and Haggard, of Scott, of Milroy, of Collip, of Davies, Haldane, and Kennaway, of Grant and Goldman, of Peters and Barr, and of others, it is known that the other six abnormal possibilities can be produced experimentally, and that at least some of them occur clinically. For this reason it has seemed desirable to enlarge the view presented in our former paper in order to include within it these conditions.

Representation of the Combined Variations in Blood Bicarbonate and Hydrion Concentration.—The blood conditions may be represented by a diagram of the type used by Haldane and others to show the "CO_2 absorption curves" of the blood, and recently further elaborated by Straub and Meier (1918) and by Haggard and Y Henderson (1919) to show also the pH values.

If we draw a curve, expressing $[BHCO_3]$ values as ordinates, and $[H_2CO_3]$ values as abscissæ, the curve will be a slanting straight line for all points corresponding to any given $[BHCO_3]:[H_2CO_3]$ ratio, and the

slant will be more or less steep according as the $[BHCO_3]:[H_2CO_3]$ ratio is great or small. But a constant $[BHCO_3]:[H_2CO_3]$ ratio indicates a constant pH (see equation of Hasselbalch below). Consequently, we are able by a series of straight, slanting lines on a diagram arranged as described to express all possible $[BHCO_3]:[H_2CO_3]$ ratios and pH values. In pure $NaHCO_3 - H_2CO_3$ solutions, the isohydrionic lines curve slightly, because the proportion of $NaHCO_3$ dissociated into Na^+ and HCO_3' increases slightly with dilution. In blood, where the Na^+ concentration is constant, the lines are practically straight. Their slope may be calculated from the equation of L. J. Henderson (1909), $[H^+] = K_1 \frac{[H_2CO_3]}{[BHCO_3]}$ or by the same equation in the logarithmic form used by Hasselbalch (1916), $pH = pK_1 + \log \frac{[BHCO_3]}{[H_2CO_3]}$. $K_1 = \frac{K}{\lambda}$, K being the dissociation constant of carbonic acid, λ the degree of dissociation of $[BHCO_3]$ into B^+ and HCO_3'. pK_1 is the negative logarithm of K_1. The value of K_1 for blood was estimated by Haggard and Henderson (1919), from the data available in the literature, as 8×10^{-8}, for which the negative logarithm, and therefore the corresponding value of pK_1, is 6.10.

The equation $pH = 6.10 + \log \frac{[BHCO_3]}{[H_2CO_3]}$ has accordingly been used in plotting the pH lines of Fig. 2 from which Figs. 3 and 4 are derived. That the value 6.10 will be subject to correction in the second decimal place as the result of further work appears probable, but it is sufficiently accurate to serve our present purposes.

For Fig. 1, since it was desired to use the customary form of CO_2 absorption curves, with total CO_2 values, $[BHCO_3 + H_2CO_3]$, as ordinates, and CO_2 tensions as abscissæ, the form of the equation used was $pH = 6.10 + \log \frac{(\text{total } CO_2) - (0.0672p)}{0.0672p}$, p being the CO_2 tension in mm. of mercury, 0.0672 the factor by which the tension is converted into terms of volumes per cent of CO_2 physically dissolved (as H_2CO_3) in the blood (Bohr, 1905).

The conditions represented by the 9 areas within the reaction range compatible with life are shown in the diagram as the following:

Area 1. Uncompensated Alkali Excess.—The condition has been observed after overdosing with sodium bicarbonate (Howland and Marriott(*b*), 1918; Harrop, 1919; Davies, Haldane, and Kennaway, 1920). It has also been caused by the loss of gastric HCl caused by obstructing the pylorus and systematically washing out the stomach for some days (MacCallum, Lintz, Vermilye, Leggett, and Boas, 1920). It is accompanied by an increase in alveolar CO_2, due to a slowing of respiration in the

apparent attempt of the organism to hold back sufficient CO_2 to restore to normal the over-alkaline reaction. There is a moderate diuresis, and bicarbonate is excreted in the urine at a rate that may be several grams per hour (Davies, Haldane, and Kennaway). Ammonia almost completely

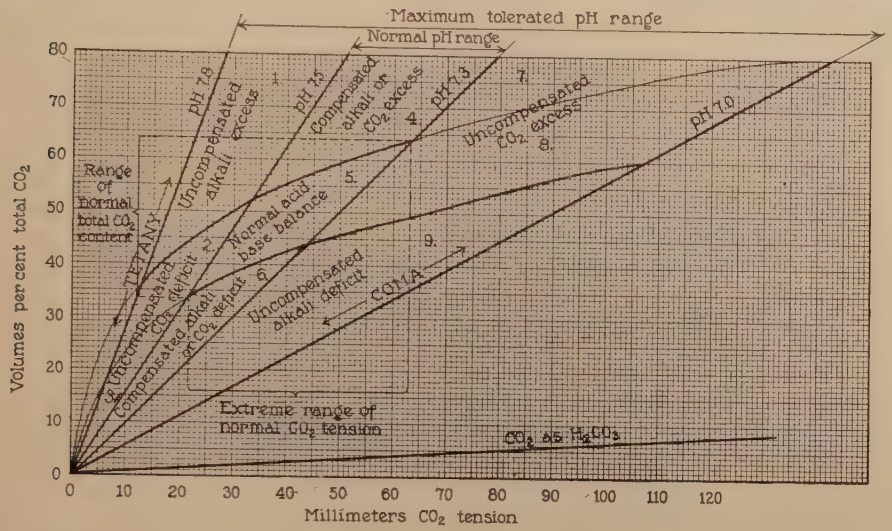

Fig. 2. Normal and abnormal variations of the $BHCO_3$, H_2CO_3, CO_2 tension, and pH in arterialized human whole blood drawn from resting subjects. The bicarbonate CO_2 at any point is obtained by subtracting from the total CO_2 the relatively small amount present as H_2CO_3 indicated by the slanting line near the bottom of the figure.

The minimum and maximum normal arterial CO_2 tensions and bicarbonate concentrations, indicated by the lower left and upper right corners of Area 5, are about twice as far from the means as are the normal extremes for these values heretofore estimated from alveolar air and arterial blood analyses. The wide range indicated by the diagram may be due to the fact that technical errors have widened in all directions the ranges indicated by the boundaries of Area 5. More accurate data will perhaps show this area to be smaller, and the extremes therefore nearer the means.

Another reason in part perhaps responsible for the fact that the extreme $BHCO_3$ and CO_2 tension values of Area 5 exceed the normally observed extremes is, that there would be only one chance out of many that maximum pH and minimum $BHCO_3$ should occur in the same individual (e.g., if levels of each so far from the mean are taken as to include only 1 individual out of 20, presumably only 1 out of 400 would show both minima at once). Consequently it would not be surprising if the extreme normal limits of CO_2 tension and $BHCO_3$ concentration have hitherto escaped observation, or have been observed so rarely as not to be regarded normal.

With more accurate technique and a larger number of observations, it appears probable that the limits of normal arterial CO_2 tension and bicarbonate concentration, indicated theoretically by a graphic estimation like the above, will coincide with those observed.

disappears from the urine, and the titratable acid may become even a negative quantity. Palmer has noted a transient albuminuria.

The most marked and characteristic clinical effect is the development of symptoms of tetany when the alkalinization proceeds sufficiently far (Howland and Marriott, 1918; Harrop, 1919; MacCallum, Lintz, Leggett, and Boas, 1920; McCann, 1918).

Compensation for the excessive bicarbonate is accomplished by a slowing of the respiration until sufficient CO_2 is held back to restore the $BHCO_3 : H_2CO_3$ ratio, and therefore the pH, to normal. The condition then shifts to that represented by Area 4. Presumably alkali excretion and inhibited ammonia formation continue until the bicarbonate also is reduced to normal, and the condition shifts back to the normal represented by Area 5.

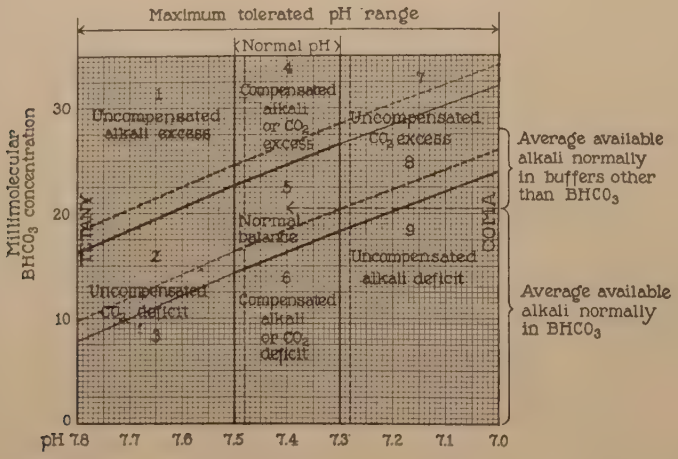

Fig. 3. Normal and abnormal variations of the bicarbonate and pH values in arterial and venous human whole blood. (The arterial conditions are indicated by the solid lines and curves, venous by the dashed lines and curves.) $BHCO_3$ and pH values are represented with rectangular coördinates, and the diagram, as compared with Figure 2, is simplified by omitting H_2CO_3 and CO_2 tension values. $BHCO_3$ values are expressed in terms of millimolecular concentration (1 millimolecular $BHCO_3$ = 2.24 volumes per cent of bicarbonate CO_2).

For a given individual it appears that the normal pH range is relatively narrow, perhaps not over 0.02, and the $BHCO_3$ range similarly narrow (Parsons, 1917; Peters and Barr, 1921); so that abnormalities in a given subject can be determined more accurately by comparison with his individual norm than by comparison with the entire Area 5, which covers normal individuals as a class.

Area 5 is approximately that covered by the nomogram of L. J. Henderson (1921, p. 414).

Although it appears certain that uncompensated alkali excess causes tetany, it is not certain that all tetany results from over-alkalinity in the blood. In the tetany caused by parathyroidectomy the results of McCann, and of MacCallum and his coworkers are at variance as to whether alkalosis exists or not.

Areas 2 and 3. Uncompensated CO_2 Deficit.—The condition has been caused in men by hyperpnea either voluntary (Collip and Backus(*b*), 1920; Davies, Haldane, and Kennaway, 1920; Grant and Goldman, 1920; Milroy, 1914), or induced by breathing air with a diminished oxygen content, such as is encountered at high altitudes (Haggard and Henderson(*d*), 1920; Haldane, Kellas, and Kennaway, 1919).

Area 2 represents the first result of lowering in blood H_2CO_3 by a respiratory stimulus other than either the blood hydrion or H_2CO_3 concentration. The consequence is an increase in the $BHCO_3 : H_2CO_3$ ratio and an overalkaline reaction (increased pH). A compensating retention of acid metabolites, indicated by a decreased excretion of ammonia and titratable acid in the urine, sets in, and there may be even an excretion of bicarbonate (Davies, Haldane, and Kennaway). As a result of these compensatory processes the bicarbonate of the blood may be lowered in some hours from Area 2 to Area 3 (partial compensation), and eventually

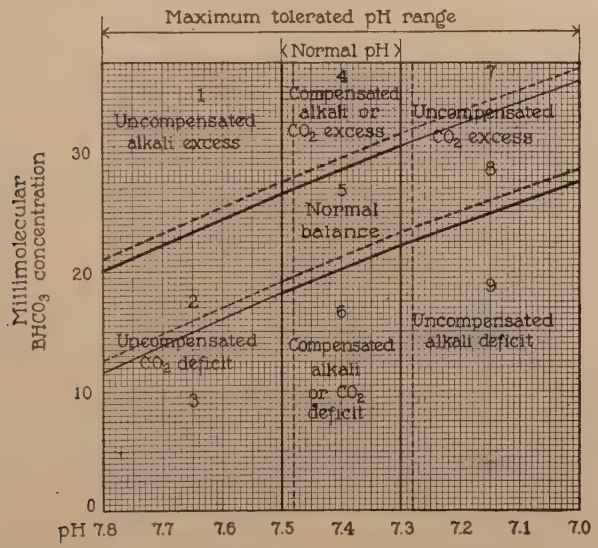

Fig. 4. Normal and abnormal variations of the $BHCO_3$ and pH in serum or oxalate plasma. Arterial conditions are indicated by the solid lines and curves, venous by the dashed lines and curves. The curves are 4 millimols higher than those of Figure 3, since the $BHCO_3$ concentration in the plasma is higher than that of the whole blood by approximately 10 volumes per cent of bicarbonate CO_2, or 4 millimols of $BHCO_3$ per liter.

to Area 6, where the pH is again down to its normal value (entire compensation). This last condition is attained when one becomes acclimatized to a high altitude (Hasselbalch and Lindhard, 1915).

The effects of uncompensated CO_2 deficit on the urine are similar qualitatively to those of uncompensated alkali excess (Davies, Haldane, and Kennaway). The rate of bicarbonate excretion observed, however, was much less (only a fraction of a gram per hour) when the blood pH was raised by overbreathing than when it was raised by administration of bicarbonate.

The ultimate clinical symptoms are again those of tetany, and have been identified as such with especial clearness by Grant and Goldman (1920). The characteristic signs after voluntary deep breathing for an

hour or less included the carpopedal spasm, Chvostek sign, Trousseau sign, Erb's sign, and in one instance even a tetanic convulsion. The physiological effects of abnormally high blood pH appear to be similar, whether the increase is caused by increase in the numerator or fall in the denominator of the $BHCO_3 : H_2CO_3$ ratio.

4. *Compensated* { *Alkali excess,* or. *CO_2 excess* Here the pH is normal, the $BHCO_3$ is high, but is balanced by a proportionally high H_2CO_3. The state of the acid-base balance of the blood is the same, whether the original disturbance was alkali retention (Area 1) or CO_2 retention (Area 7-8). Hence the condition may be described as either compensated alkali excess or compensated CO_2 excess, according to whether the primary disturbance is due to alkali excess or CO_2 excess.

The condition has been observed to arise from both causes. *Alkali excess* is most commonly caused by therapeutic administration of sodium bicarbonate. If, as is usually the case following oral administration, the absorption is not rapid, CO_2 may be retained sufficiently to balance the increased $BHCO_3$, and the condition moves from that indicated by Area 5 to that of Area 4. If absorption is too rapid for simultaneous compensation by CO_2 retention, the condition changes to that indicated by Area 1.

Compensated *CO_2 excess* is, it appears, the state observed by Scott(*b*) (1920) in emphysema. The retarded gas exchange presumably leads to a state of chronically increased CO_2 tension in the blood, and the body raises the blood $BHCO_3$ high enough to balance the H_2CO_3 and maintain a normal reaction.

It appears that this condition, primarily due to CO_2 retention, may be differentiated from that in which alkali retention is the primary cause, by the fact that a primarily respiratory CO_2 retention is associated with cyanosis, either permanent or caused by slight exertion. Diffusion of oxygen through membranes is so much slower than that of CO_2 (Krogh(*a*), 1919) that any hindrance retarding the alveolar gas exchange sufficiently to affect CO_2 excretion would presumably be accompanied by still more hindrance to oxygenation of the blood. This presumption is further supported by the work of Krogh and Krogh (1910) who found in rabbits that while CO_2 tension in arterial blood and alveolar air are equal, oxygen tension is lower, even when respiration is unhindered.

Area 5. Normal Acid-Base Balance.—The normal area represents the balance that is practically always found in the resting individual in health and at ordinary altitudes. It is possible that when the normal pH limits of the plasma are more accurately defined, they may fall within a narrower range. Parsons is inclined to place the normal range at more nearly between pH 7.30 and 7.40 than the doubly wide range of 7.30-7.50 which

we have allowed, chiefly on the basis of data yielded by CO_2 absorption curves of whole blood.

Area 6. Compensated { *Alkali deficit,* or. *CO_2 deficit* } The blood condition represented by Area 6 is that commonly observed in the acidoses of metabolic diseases, in diabetes, nephritis, infant marasmus. Until recently it has been the only form of naturally occurring acidosis observed clinically, except in the premortal state. Since the pH is normal, the alkali neutralized by the invading acids is solely that of the bicarbonate (see page 63) and the fall in blood bicarbonate is an exact measure of the acid that enters the blood. For the reason that this condition at the time represented all clinically observed acidoses, Van Slyke and Cullen in 1917 defined lowered blood bicarbonate as characteristic of acidosis. The definition is adequate for compensated alkali deficit, but it is not sufficient to cover the conditions since observed which are represented by Areas 7, 8, and 9, and which are likewise caused by acid retention, and by Areas 2 and 3, in which the bicarbonate is reduced without acid retention.

As the result of accelerated production of acids (diabetes) or retarded elimination (presumably the case in nephritis) the alkali reserve of the entire body is diminished, that of the blood falling parallel with that of the other body fluids. In experimental acid intoxication Goto(*c*)(1918) has found that the potassium phosphate of the tissues and the $CaCO_3$ of the bones are also reduced.

In the evident attempt to maintain a normal $H_2CO_3 : BHCO_3$ ratio and blood pH, ventilation becomes deeper, and the H_2CO_3 is reduced in proportion to the $BHCO_3$. Presumably there is during the acid invasion a slight increase in hydrogen ion concentration, causing the blood condition to shift toward the border of Areas 6 and 9. The respiratory center is, however, at once stimulated, and CO_2 is driven off so that the condition remains in Area 6.

The path above delineated is not the only one by which Area 6 is reached. A compensated fall of blood alkali may also occur when the primary cause is not acid retention, but excessive respiratory loss of CO_2. In this case the fall in blood bicarbonate is a compensatory process which tends to prevent the blood reaction from becoming abnormally alkaline. One respiratory stimulant which has, we believe, been satisfactorily demonstrated to have such an effect is oxygen want. Y. Henderson (1920) has shown from data obtained by Fitzgerald, and by Douglas, Haldane, Henderson, and Schneider on their Pike's Peak expedition that the CO_2 of the alveolar air is lowered at high altitudes, and varies in direct proportion to the barometric pressure. This is also shown by the data of Hasselbalch and Lindhard (1915). Since the rate of CO_2 production is not lowered (Hasselbalch and Lindhard), it is evident that the minute volume of air breathed is increased, an effect which is also noted when

air with reduced oxygen percentage is breathed at sea level pressure.

The process by which the state of compensated CO_2 deficit is reached has been outlined in the discussion of the condition represented by Areas 2 and 3.

The final effect, lowered bicarbonate with normal pH, is the same as in compensated alkali deficit caused by retention of non-volatile acids. The primary cause in compensated CO_2 deficit, however, is not acid retention, but loss of an acid (carbonic), which is subsequently compensated by a reduction of the blood alkali.

Area 7-8. Uncompensated CO_2 Excess.—In this condition respiratory excretion of CO_2 is retarded, either by physical hindrance or by deadening of the respiratory center, so that H_2CO_3 of the blood is raised. In consequence the $BHCO_3 : H_2CO_3$ ratio and the pH are lowered. The actual blood reaction becomes less alkaline than normal.

This condition has been caused experimentally by breathing air which contains 3 to 5 per cent of CO_2 (Hasselbalch and Lundsgaard, 1912; Davies, Haldane, and Kennaway, 1920). It appears to be caused also when the respiratory center is deadened by morphin narcosis (Henderson and Haggard, 1917, a).

Clinically Means, Bock, and Woodwell (1921) report observation of the condition in a cyanotic pneumonia patient.

The physiological effects are seen in an accelerated excretion of ammonia and titratable acid by the urine, the same effects observed when the acid-base balance is upset by retention of non-volatile acids. Davies, Haldane, and Kennaway (1920) observed a doubling of the rate of ammonia and titratable acid excretion after breathing air containing up to 5 per cent of CO_2. There is also, as in non-volatile acid retention, an increase in the minute volume of air expired, in the apparent attempt to get rid of the excess of H_2CO_3 unless the respiratory center is deadened (as by morphin).

The first effect of CO_2 retention on the blood is to increase the H_2CO_3 and H^+ of the blood, without changing the buffer alkali content (condition represented by Area 8). Thus Davies, Haldane, and Kennaway found after breathing for an hour air containing CO_2 in amounts gradually increasing up to 5 per cent, there was no change in the CO_2 capacity of the blood (unchanged total buffer alkali). Henderson and Haggard (1917) found that in dogs a rise of 2 or more volumes per cent in CO_2 capacity of the blood within a half hour after injecting morphin, or breathing air containing 5 or more per cent of CO_2.

This increase in the blood alkali secondary to H_2CO_3 increase is compensatory in its nature, it tends to raise the $BHCO_3 : H_2CO_3$ ratio back to normal by increasing the $BHCO_3$ to balance the increased H_2CO_3. In consequence the blood condition tends to shift from Area 8 to Area 7

(partial compensation) and thence over to Area 4 (complete compensation).

The compensatory increment of blood alkali probably comes from two sources: (1) The increased excretion of ammonia and titratable acid through the kidneys tends to raise the bicarbonate content of the entire body, and the blood plasma bicarbonate would normally rise with that of the other fluids. (2) HCl may, perhaps, leave the blood plasma and enter the tissue cells, as it has been shown to leave the plasma and enter the blood cells when the pH rises (Reaction 1 of the diagram on p. 61). The rate of blood alkali rise observed by Henderson and Haggard appears too rapid to be accounted for by acid excretion alone, and these authors attribute the increase to alkali drawn from the tissues. The effect would be the same if acid passes from the blood into the tissues, a process which from analogy with the shift between plasma and blood cells seems more probable. The relative parts that these two factors, acid excretion and shift of acid to the tissues (or of alkali in the reverse direction), play in the compensatory rise of blood bicarbonate during CO_2 retention is uncertain. That accelerated acid excretion occurs has been shown. That acid shift from blood to tissues also occurs seems probable.

Increased blood bicarbonate due to compensation of CO_2 retention may, it appears, be clinically differentiated from that due primarily to alkali excess by the fact that CO_2 retention is accompanied by cyanosis (see also discussion of Area 4). This has been observed by Means, Bock, and Woodwell in the cases cited above.

Area 9. Uncompensated Alkali Deficit.—This is the condition defined by Hasselbalch and Gammeltoft (1915) as "uncompensated acidosis." It has been most frequently observed in cases of nephritic and diabetic acidosis in the premortal period. Means, Bock, and Woodwell (1921) describe most completely both the symptoms and blood changes in such a nephritic case. The blood bicarbonate is extremely low. Respiration, which up to the terminal stage has kept the H_2CO_3 sufficiently low to maintain a normal H_2CO_3:$BHCO_3$ ratio, now fails to do so, and the blood condition shifts from that represented by Area 6 over into that represented by Area 9.

In deep ether anesthesia, according to the results of Van Slyke, Austin, and Cullen (1920) and in certain cardiac patients (Peters and Barr, 1921), the blood state is represented by Area 9, and both alkali deficit and carbonic acid retention occur.

Relation of Changes in the Acid-Base Balance of the Blood to Changes in the Other Body Fluids

As has been already shown, the intercellular fluids other than blood plasma have, so far as studied, been found under normal conditions to approximate the blood plasma in bicarbonate and hydrion concentrations. There is evidence that in changes from the normal the other body fluids follow more or less promptly the blood plasma. Van Slyke and Cullen (1917) found that when acid was injected into the circulation the fall in blood bicarbonate was only about one-sixth as great as it would have been had the acid all remained in the blood; the other five-sixths of the acid must have gone into the other body fluids and the tissues, or drawn alkali from them. Palmer and Van Slyke (1918) found similarly that when bicarbonate is administered, the rise in blood bicarbonate was approximately that calculated on the assumption that the alkali was not retained in the blood, but was distributed evenly through all the body fluids. Collip and Backus(*a*)(1920) found the bicarbonate of the spinal fluid follows that of the venous blood plasma. When the latter was lowered by continued etherization, or by shock (handling of intestines) the bicarbonate of the spinal fluid also fell and to about the same level, although more slowly. When the alkali reserve of the blood was raised by bicarbonate injection, the spinal fluid bicarbonate rose in the course of a few hours to approximately the same level.

Methods for Determining the State of Acid-Base Balance of the Body

The available methods may be classified as either functional or direct. In the former the presence of one or more of the functional abnormalities caused by acidosis is taken as evidence of its existence. The functional abnormalities thus used really represent unusual efforts of the organism to regain a normal acid-base balance. The effort is likely to vary in intensity as the degree of the disturbance in the balance, and hence to indicate with some degree of accuracy the severity of the disturbance. Such an effort is the hyperpnea of acidosis with the resultant lowering of the alveolar CO_2 tension, in the obvious attempt to lower the blood H_2CO_3 and maintain thereby a normal pH. Such an effort also is the increased hourly excretion of ammonia and titratable acid in the urine, and of the specific acids responsible for the disturbance, as in the ketonuria of diabetes. Observations of such functional activities are and will be of value in detecting acidosis, but they contain an inherent source of error in that they presuppose a normal response of the respective functions to the

acidosis. If the particular function studied itself is affected, as is respiration in narcosis or renal secretion in nephritis, it may utterly fail to indicate an acidosis that is present. On the other hand, it is at least theoretically possible for it to indicate an acidosis that is absent, if the function is stimulated by some other factor. The alveolar CO_2 tension, for example, may be lowered by respiratory stimuli other than the blood hydrion concentration. It is known to be lowered by diminution of the oxygen tension of the air, also by voluntary deep breathing and by deep breathing caused by psychic disturbance.

The direct methods are those by which the acid-base balance of the body itself, or of the blood as representative of the body, is studied. They include the determination of the $BHCO_3$ and pH in the blood, and the alkali retention test as performed by Palmer, Salvesen, and Jackson. The results of observations by such methods are not likely to be falsified by functional stimuli or inhibitions, and they furthermore may be made to indicate the amount by which the body's buffer alkali content is changed. The direct methods appear therefore less subject to error and more subject to quantitative interpretation than the functional, and we shall consider them first and in more detail.

1. Estimation of the Blood Bicarbonate and pH.—For the most complete information which we are able to interpret concerning the state of the acid-base balance of the blood, it is sufficient to determine quantitatively any two of the three variables pH, $BHCO_3$, and H_2CO_3 (or CO_2 tension). For if two are fixed, they determine the other, which may be calculated from them by the equation $H^+ = K_1 \times \frac{H_2CO_3}{BHCO_3}$, or $pH = pK_1 + \log \frac{BHCO_3}{H_2CO_3}$.

In the form of acidosis of most frequent clinical occurrence, compensated alkali deficit, such as is usually found in diabetes, nephritis, and the acidoses of children, the pH remains normal, the bicarbonate alone is altered, and its change affords complete evidence for diagnosis. For this reason the technique for plasma bicarbonate determination introduced by Van Slyke and Cullen (1917) has proven fairly adequate for the study of the acid-base balance in these conditions.

The preceding résumé of the possible states of the acid-base balance of the blood, however, shows that conditions are now known, some of which may be encountered clinically, in which the pH is not normal, and which, therefore, the bicarbonate alone does not suffice to show. It would be impossible, for example, to tell whether a high blood bicarbonate indicated the condition signified in Figure II by Area 1, Area 4, Area 7, or the upper portion of Area 8, unless other data were available. A knowledge of either the pH, or the H_2CO_3, however, in addition to the bicarbonate

would accurately locate the point on a diagram like that of Figure II, and would indicate the nature of the blood condition.

Of the three values, the two which are most simply and accurately determined by the technique available are the bicarbonate concentration and the pH. The third value, the H_2CO_3, requires at present for its estimation a plotting of the CO_2 absorption curve of the blood examined, and for reliable results the determinations involved, which include a correction for the oxygen unsaturation of the hemoglobin, make unusual demands on both time and skill. CO_2 absorption curves of clinical cases have nevertheless yielded results of decided interest in the hands of Peters and Barr (1921) and of Means, Bock, and Woodwell (1921), and the reader is referred to Peters and Barr for the technique. In their work, absorption curves were desirable to throw light on questions of respiratory pathology, in particular on CO_2 tension equilibria between blood and alveolar air, as well as on the acid-base balance.

For determination of the acid-base balance, however, we can simplify both the technique and the diagram for interpreting results by leaving out the H_2CO_3 and devoting our attention to the $BHCO_3$ and the pH. If we plot curves showing the possible blood conditions, with the $BHCO_3$ values as ordinates, the pH or H^+ values as abscissæ, we obtain Figure 3 for whole blood and Figure 4 for plasma.

For the complete technique of the pH and $BHCO_3$ determinations the reader is advised to consult the original papers cited below. We shall, however, outline the principles on which the methods are based, and the more especial precautions required when they are applied to the blood.

Collection and Treatment of Blood Samples.—In collecting and handling blood, the following precautions are of importance:

(1) For at least one hour before the blood is drawn the subject should avoid vigorous muscular exertion, as this, presumably because of the lactic acid formed, lowers the bicarbonate of the blood (Christiansen, Douglas, and Haldane, 1914; Morowitz and Walker, 1914). It also appreciably lowers the pH (Parson, Parsons, and Barcroft, 1920).

(2) If venous blood is used undue accumulation of CO_2 is avoided by avoidance of stasis, and by keeping warm the arm from which the blood is drawn.

(3) Within an hour or two after human blood is drawn the cells begin to form acid products (Christiansen, Douglas, and Haldane, 1914) with a resultant fall in both pH and bicarbonate. Consequently one must either analyze the whole blood within an hour after it leaves the body, or centrifugate it within that time and perform the analyses on the plasma.

(4) No opportunity must be given for escape of CO_2, either when the blood is drawn or during its subsequent handling, or the pH will rise and the bicarbonate will fall. Exposure to air must be entirely avoided. A layer of paraffin oil over blood in a tube standing quietly prevents ap-

preciable loss of CO_2 for an hour or more. If the blood is kept longer, or is agitated, as in centrifugation, paraffin oil is insufficient protection. A layer of solid paraffin (melting point 40-45°) may be used, or the tube may be filled with blood entirely to the stopper, so that no air space is left.

Van Slyke and Cullen (1917) used the precaution of saturating plasma immediately before analysis with CO_2 at normal alveolar tension, in order to prevent errors from escape of CO_2 during the period between centrifugation and analysis. With the precautions for handling the plasma and the mode of calculation below outlined, however, such resaturation becomes unnecessary.

Gasometric Determination of Whole Blood or Plasma Bicarbonate.— In either the whole blood or plasma the total CO_2 may be determined gasometrically and the portion in the form of $BHCO_3$, which is normally about 95 per cent of the total, may be estimated from the pH.

For determination of the total CO_2 Haldane (1920) adds acid to the blood in a closed vessel connected with a sensitive manometer, and estimates from the rise in pressure the amount of CO_2 set free. Y. Henderson (1917) similarly adds acid to the blood in a relatively large closed vessel, but measures the CO_2 evolved by running the air-CO_2 mixture from the vessel into a gas burette, where the CO_2 is determined by analysis.

Van Slyke (1917), in a method later refined by Van Slyke and Stadie (1921), adds acid to the blood in a 50 c.c. pipette provided with stopcocks at both ends. The entire space in the pipette, except that occupied by the blood and acid, is filled with mercury, and the lower end of the pipette is connected with a leveling bulb. By lowering the latter the mercury is drawn out of the pipette, and a Toricellian vacuum obtained in it. The escape of CO_2 into the vacuum is so rapid that it is complete in about 30 seconds. The mercury is then readmitted and the volume of CO_2 is read in the upper stem of the pipette, which is calibrated for the purpose.

Each of the above three methods may be used with 1 c.c. or less of blood or plasma, and each has given satisfactory results in the hands both of its originator and of other investigators.

From the total CO_2 content determined by any of these methods the $BHCO_3$ may be calculated by Table I.

The table is computed from the equation $pH = pK_1 + \log \frac{BHCO_3}{H_2CO_3}$, pK_1 having the value 6.15 for whole blood, 6.10 for plasma. Substituting R for the ratio $\frac{BHCO_3}{H_2CO_3}$, we have $\log R = pH - pK_1$ and $\frac{100\ BHCO_3}{BHCO_3 + H_2CO_3} = \frac{100\ R}{R+1}$ = per cent of total CO_2 as $BHCO_3$. From

TABLE I

PERCENTAGE OF CO_2 IN THE FORM OF BICARBONATE AT DIFFERENT pH LEVELS

Plasma pH	Per Cent of Total CO_2 as $BHCO_3$	
	Whole Blood	Plasma
7.0	87.7	88.8
7.1	88.9	90.8
7.2	91.8	92.6
7.3	93.4	94.1
7.4	94.7	95.2
7.5	95.7	96.1
7.6	96.6	97.0
7.7	97.3	97.6
7.8	97.8	98.1

the values of R calculated from the equation $\log R = pH - pK_1$ Table I is computed.

Titrimetric Determination of Plasma or Serum Bicarbonate.—The plasma or serum (1 c.c.) is acidified with 1 c.c. of N/20 HCl, and is completely freed from CO_2 by whirling the acidified mixture about the inner wall of a small round flask for 1 or 2 minutes. The mixture is then titrated back to the initial pH of the plasma with N/100 NaOH, phenol red being used as indicator. Since at the same pH every buffer acid, other than the escaped carbonic, binds the same amount of alkali as before the titration, the effect of the titration is merely to change all the $BHCO_3$ to BCl, and the HCl utilized is equivalent to the $BHCO_3$ (Van Slyke, Stillman, and Cullen, 1919; Stillman(*b*), 1919; Van Slyke (*h*), 1921). All the solutions used are made up in 0.9 per cent NaCl solution instead of in water. At the end of the titration the volume is brought up to 15 c.c. by addition of 0.9 per cent NaCl solution.

The end point is ascertained by comparing the color of the titrated solution with that of a control tube prepared by mixing under paraffin oil 1 c.c. of plasma with 14 c.c. of 0.9 per cent NaCl solution.

Electrometric Determination of the Plasma pH.—The electrometric determination is the standard on which others are based. For a description of both principle and technique, which cannot be taken up here, see W. M. Clark's recent work (1920). As shown by Parsons (1917) the pH actually determined is that of the plasma, whether the corpuscles are suspended in it or are absent. All blood pH figures which are at present available therefore represent the plasma pH. This is true even when the pH is calculated from the $BHCO_3 : H_2CO_3$ ratio, since the constant of Hasselbalch's equation is based on electrometric determinations. The pH of the cell contents is presumably a little lower (Michaelis and Davidoff, 1912). That it parallels that of the plasma, however, is shown by the fact that change in the $BHCO_3 : H_2CO_3$ ratio of the cells parallels that of the plasma (Joffe and Poulton, 1920; Fridericia(*b*), 1920).

Colorimetric Dialysis Method for pH.—For the general technique and principle of colorimetric methods the reader is again referred to Clark (1920). The color of the blood obviously makes impossible a determination directly in it. Levy, Rowntree, and Marriott (1915) obviated the difficulty by dialyzing the fresh blood in a collodion sack suspended in a test tube of water. The pH of the water increases and within a few minutes reaches constancy at a point near that of normal blood, which at room temperature is 7.5 to 7.6, about 0.2 higher than at 38°. Dale and Evans (1920) have recently elaborated the Levy, Rowntree, and Marriott method by protecting both blood and diffusate from loss of CO_2 by layers of paraffin oil. Such a technique may give accurate comparative results, but controlling of the results with those obtained directly on the blood by the electrometric method still remains to be done, and is necessary before the data on the diffusate can be accurately compared with those based on the electrometric method.

Direct Colorimetric Method for Plasma pH.—A technique for determining the pH directly on diluted plasma has been perfected by Cullen, and is about to appear in the *Journal of Biological Chemistry* (1922). It gives the same results as the electrometric method.

The Alkali Retention Test for Alkali Deficit

This test rests on the facts that when the bicarbonate of the body fluids is lowered by retention of non-volatile acid, acid urine is excreted, and sufficient alkali must be given and absorbed to raise the bicarbonate concentration in the body fluids to a normal level before the pH of the urine begins to increase.

The above facts have been established by a series of investigations. Palmer and Henderson (1913) and Sellards (1912) independently observed that 5 or 10 grams of sodium bicarbonate taken by mouth usually suffice to turn the urine of a normal adult alkaline, but that in nephritic or diabetic acidosis 50 to 100 grams may be required. Palmer and Van Slyke (1917) found that the urine of normal men approaches the alkalinity of the blood (pH 7.4) when the plasma bicarbonate CO_2 is caused to rise above 71 ± 5 volumes per cent. In many pathological cases, however, the urine failed to rise to pH 7.4 when the plasma bicarbonate was raised to even higher levels, so that if a urinary pH of 7.4 were taken as the end point, so to speak, of the titration of the body's alkali deficit, a deficit might be indicated where none existed. Also a harmful excess of alkali might be administered before the urinary pH reached 7.4. Recently, however, Palmer, Salvesen, and Jackson (1920) have shown that if the end point taken is the *first rise* in the urinary pH, the above source of error is obviated. The first rise in urinary pH was noted in both normal

and pathological cases when the plasma bicarbonate CO_2 approached 69 ± 10 volumes per cent.

The test is so simple that we can describe it in sufficient detail here. It is performed by administering sodium bicarbonate dissolved in water at the rate of a dose of 2 to 5 grams every half hour. Two samples of 1 c.c. each of urine obtained before the first dose are diluted in test tubes to 25 c.c. each with distilled water. To one sample 10 drops of 0.04 per cent phenolsulphonephthalein are added, to the other 10 drops of a saturated solution of methyl red. Before giving each dose of bicarbonate another sample of urine is drawn and treated in the same way. The first definite change towards alkalinity shown by comparison with the original urine samples marks the end point. Phenolsulphonephthalein serves to show changes between pH 6.3 and 7.4, methyl red between 4.7 and 6.3, so that the two indicators cover the entire range of urine reaction.

Usually 0.2 gram or less of bicarbonate per kilo of body weight causes a change in urinary pH when no acidosis is present. More than 0.5 gram per kilo indicates marked alkali deficit, and more than 1.0 gram a condition that may threaten coma.

The test would, it appears certain, be interfered with by conditions altering the sensitiveness of the respiratory center, and therefore the blood pH. For example, over-ventilation by itself is sufficient to raise the pH of both blood and urine, even though the alkali content of the blood is not increased, and the reverse is true of depressed respiration. In the acidosis usually encountered in metabolic diseases, with diminished blood alkali but normal respiratory control (Area 6 and the lower part of 9, Figure 2) the bicarbonate retention test indicates simply and reliably the acid-base balance of the body. Also, when alkali deficit exists, the therapeutic agent (bicarbonate) is administered as part of the procedure in the required amount to correct the deficit.

Determination of the Alveolar CO_2 Tension[3]

When the gas exchange in the lungs is normal, the alveolar air, as shown by A. and M. Krogh, is in equilibrium in respect to its carbon dioxid content with the arterial blood. Consequently, in accordance with the law of gas solubilities, the concentration, or tension, of CO_2 in the alveolar air is directly proportional to that of the free carbonic acid (H_2CO_3) in the blood. And when the blood pH is normal and constant, the H_2CO_3

[3] The "tension" is commonly used as the unit of concentration of the alveolar gases. Pure dry CO_2 at average atmospheric pressure has a tension of 760 mm. If the gas is saturated with moisture at 38°, at which temperature the vapor tension is 49 mm., the total dry gas tension is $760 - 49 = 711$ mm. Moist air containing 5.6 per cent of CO_2 at 38°, 760 mm. (as does an ordinary alveolar air sample) has a CO_2 tension of $0.056 \times 711 = 40$ mm.

bears a constant relation (of about 1:20) to the $BHCO_3$. All three concentrations go up and down together, the blood $BHCO_3$ fixing the level of the H_2CO_3, and the latter that of the alveolar CO_2. Consequently the alveolar CO_2 tension is normally proportional to the blood bicarbonate.

This proportionality fails when for any reason, such as narcosis of the respiratory center, respiratory stimulus by oxygen want, excitement, or other factors (Van Slyke and Cullen, 1917, p. 299), the ratio $BHCO_3 : H_2CO_3$ in the blood plasma becomes variable, or when the gas exchange in the lungs is mechanically retarded sufficiently to prevent approximately complete CO_2 equilibrium between them, as seems to occur in certain cardiac conditions (Peters and Barr, 1920).

The determination is made by determining the CO_2 content of a sample of expired air collected in one of two ways.

By the technique of Haldane and Priestley (1905) the subject, having been breathing normally, suddenly empties his lungs as completely is possible, the last air expired being analyzed. The CO_2 tension thus determined approximates that of the arterial blood. The simplest technique for collecting and analyzing the air is probably that of Fridericia(*a*) (1914). The subject expires through a 100 c.c. pipette that can be closed by cocks at both ends. Alkali solution is admitted, which absorbs and displaces the CO_2, the c.c. of gas displaced by the solution indicating the percentage of CO_2.

With the technique of Plesch (1909) the subject breathes in and out of a bag for 20 or 30 seconds, and the air in the bag is analyzed. The CO_2 tension is believed to approximate that of the venous blood. For its determination Marriott(*b*)(1916) has devised a most convenient colorimetric method. The gas from the bag is bubbled through 2 or 3 c.c. of 0.01 $\overline{N}$ NaOH solution colored with phenolsulphonephthalein. The NaOH is quickly changed to $NaHCO_3$, and in 1 or 2 minutes a permanent $NaHCO_3 : H_2CO_3$ ratio is established. The H_2CO_3, and therefore the hydrion concentration, is proportionate to the CO_2 content of the air. By comparison with a series of standard tubes over the proper pH range, the CO_2 tension of the air may be estimated from the color of the solution.

Determination of the Excretion Rate of Ammonia and Free Acid

The sum of ammonia plus titratable acid in the urine represents the excretion of acid in excess of mineral bases. The normal excretory reaction of the organism to lowered blood pH or lowered alkaline reserve is an increase in excretion of ammonia and titratable acid. Fitz and Van Slyke (1917) and Van Slyke (1918) have shown that in diabetic acidosis the 24 hour excretion of ammonia and titratable acid increases approximately

as the square of the fall in plasma bicarbonate below the point indicated by 80 volumes per cent of CO_2 as indicated by the equation

$$0.1\ N\ acid + NH_3\ per\ kilo\ body\ weight = \left(\frac{80 - plasma\ CO_2}{5}\right)^2$$

The clinical significance of varying excretion rates in at least this one form of acidosis (diabetic) is indicated by Table II. In diabetes the excretion follows the fall in alkaline reserve with sufficient regularity to form a semi-quantitative measure of the latter.

In nephritis the ammonia plus acid excretion appears to bear no relation to the alkali reserve.

Determination of Acetone Bodies in the Blood and Urine

In diabetes and apparently also in fasting and in the cyclic vomiting of children, acidoses occur which are entirely due to rapid formation of the "acetone bodies," β-hydroxybutyric acid, and acetoacetic acids. Their source is incompletely burned fatty-acids, and in diabetes 36 per cent of the fat consumed may be excreted as acetone bodies (Magnus-Levy, 1905). Their formation, in diabetes at least, is attributed by Magnus-Levy to combustion of fatty acids without the simultaneous combustion of sufficient carbohydrate, the latter being necessary, for some still unexplained reason, to complete combustion of the fats. Ladd and Palmer (1921) have confirmed this explanation. They find that acetone bodies are formed by diabetics as by normal persons, when the ratio of calories fat to calories carbohydrate burned exceeds about 10 to 1, so that the cause of ketonuria in diabetes is not primarily failure in the fat-burning mechanism, but secondary failure in fat combustion due primarily to failure in sugar combustion. The acidosis of fasting has the same origin; the body consumes its carbohydrate so rapidly that after a short fast it no longer has sufficient to supply the necessary 1 to 10 ratio for the combustion of fat. The ketonuria of the toxemias of pregnancy is presumably due to fasting (Van Slyke and Losee, 1917), and has been shown by Duncan and Harding (1918) to be remedied by administration of lactose.

In cyclic vomiting of children, however, ketonuria occurs without previous evidence of malnutrition, and we are entirely ignorant of its primary metabolic cause.

Ketone formation has two significances: it indicates incomplete fatty acid combustion; and it indicates the formation of acid products which may lead to an abnormal state in the acid-base balance of the body.

Quantitative determinations of the acetone bodies in the urine (Van Slyke(*e*), 1917) and blood (Van Slyke and Fitz(*a*)(*b*), 1917 and 1919) are chiefly of value to indicate the extent of the failure in fatty acid metabolism and to assist in its dietary control. They do not indicate very

TABLE II

COMPARISON OF CLINICAL CONDITION IN DIABETIC ACIDOSIS WITH RESULTS OF DIFFERENT TESTS FOR ALKALI DEFICIT *

Condition of Subject	Plasma Bicarbonate			Alkali Retention***		Acid Excretion Rate****		CO_2 of Alveolar Air
	Actual		By CO_2 Capacity Method of Van Slyke and Cullen**	Sodium Bicarbonate by Mouth Required to Increase pH of the Urine		0.1 N Acid + NH_3 = per 24 hour time unit		
	Vol. per cent bicarbonate CO_2	*Mol. Conc.*	*Vol. per cent bicarbonate CO_2*	*Gm. per kg.*	*Approximate gm. per 60 kg. Person*	*C.c. per kg.*	*Approximate c.c. per 60 kg. Person*	*mm. tension*
Normal resting adult. Extreme limits.	70-48	0.031-.021	80-53	0.0-0.4	0.0-25	0-27	0-1,600	50-35
Mild acidosis. No pronounced symptoms.	48-36	.021-.016	53-40	0.4-0.8	25-50	27-65	1,600-4,000	35-27
Moderate to severe acidosis. Symptoms may be apparent.	36-25	.016-.011	40-30	0.8-1.1	50-65	65-100	4,000-6,000	27-20
Severe acidosis. Symptoms of acid intoxication.	Below 25	Below .011	Below 30	Over 1.1	Over 65	Over 100	Over 6,000	Below 20

* From the results of Stillman, Van Slyke, Cullen, and Fitz, 1917.

** The normal bicarbonate CO_2 is raised approximately one-tenth by resaturating the plasma at 20°, according to the technique of Van Slyke and Cullen (1917, pp. 326-327), the effect being somewhat greater when the bicarbonate is abnormally low.

*** The figures recorded in this column indicate also the doses of $NaHCO_3$ necessary to restore the alkali reserve to normal. The maximum normal dose is given as 0.4 gm. per kg., but the usual normal is less than 0.2.

**** After alkali administration the acid excretion rate indicates greater alkali deficit than exists. (Stillman, Van Slyke, Cullen, and Fitz, 1917.)

accurately the condition of the acid-base balance of the body, which may be normal even when large amounts of acetone bodies are being excreted. The daily excretion of the acetone bodies may be followed with sufficient accuracy for most purposes, in diabetes at least, by means of the simple organic acid titration method of Van Slyke and Palmer (1920).

As a test for acidosis caused by the ketone bodies, qualitative determinations of the acetone or acetoacetic acid in the urine are significant so long as they are negative. A diabetic with no acetone in the urine may be assumed to have a normal alkaline reserve. The appearance of acetone bodies, however, is only a sign of abnormal fatty acid combustion, which may or may not lead to an alkali deficit.

Diagnosis and Therapy in the More Frequent Types of Acidosis

General Considerations Concerning Diagnosis.—In a clinical condition that has not been studied completely enough to permit taking for granted any of the factors involved, the state of the acid-base balance can be ascertained only by determining both the bicarbonate and the pH of the blood. For example, lack of simultaneous determinations of both factors leaves us at present uncertain as to whether the lowered plasma bicarbonate observed by Cannon(*a*)(*b*)(1918) in traumatic shock indicates a genuine deficit in the available alkali of the body (Areas 6 or 9, Fig. II) caused primarily by retention of non-volatile acids, or whether the condition is one of CO_2 deficit due primarily to hyperpnea (Area 3, Fig. II) and leading not to acidification but to alkalinization of the body, as believed by Y. Henderson and Haggard(*d*)(1918).

If, however, it is established that the acidosis occurring in a given clinical condition is always of one type (e. g., the ketosis of diabetes) the test of patients in this condition may, with relatively small chance of error, be reduced to the simplest technique that will reveal the type of acid-base disturbance ordinarily encountered. Thus tests for acetone in the urine are of value in excluding acidosis in diabetes, but useless in the marasmus of infants.

General Considerations Concerning Therapy.—Acidosis is a by-product of disordered metabolism. Measures against it, in order to be of more than transitory benefit, must therefore correct the abnormal condition from which the acidosis is a secondary result.

Nevertheless it appears that the acidosis itself may at times, as in threatened diabetic coma, become so acute that measures aimed at the immediate, even though temporary, restoration of the acid-base balance are indicated in order to prolong life. As such a measure the administration

of sodium bicarbonate, introduced by Magnus-Levy(*e*)(1899), appears justified both by logic and practice.

In the administration of bicarbonate the following precautions are indicated:

(1) Bicarbonate is to be given only when a genuine alkali deficit exists in the body, as shown by a blood condition indicated by Areas 6 or 9, Fig. II.

(2) Only sufficient bicarbonate is to be given to restore the normal blood alkali content. Even this amount may result in edema, from the increase in the amount of dissolved salts (chlorid and bicarbonate) in the body fluids. If unnecessarily great amounts of bicarbonate are given, the probability of edema is increased.

Another result of overdosage with bicarbonate is tetany, which apparently is caused by abnormally high pH, the condition of "uncompensated alkali excess" indicated by Area 1, Fig. II.

The amount of sodium bicarbonate required to restore the normal alkaline reserve may be estimated by the formula of Palmer and Van Slyke (1918) from the plasma bicarbonate CO_2 content. Grams $NaHCO_3 = (60 - \text{plasma } CO_2) \times \frac{\text{Weight in Kilos}}{38}$, the plasma CO_2 being expressed in terms of volumes per cent.

The formula is derived as follows: 1 gm. of $NaHCO_3$ contains 267 c.c. of CO_2, measured at 0°, 760 mm. If the body fluids are estimated at 700 c.c. for each kilo of body weight then the distribution of 1 gram of bicarbonate among them would raise the CO_2 content, in c.c. per 100 c.c. of fluid, by $\frac{267}{7\,W} = \frac{38}{W}$ c.c., W representing the body weight in kilos. Conversely, the amount of bicarbonate necessary to raise the CO_2 by b volumes per cent would be $\frac{b\,W}{38}$. If $b = 60 -$ plasma CO_2, the amount by which the bicarbonate CO_2 in the plasma has fallen below 60 volumes per cent, then the bicarbonate required to raise it back to 60 would be $\frac{W}{38} \times (60 - \text{plasma } CO_2)$. The approximate accuracy of this equation has been demonstrated by Palmer and Van Slyke (1918), and by Palmer, Salvesen, and Jackson (1921).

Overdosage with alkali may be avoided by estimating the amount required from the plasma bicarbonate CO_2 in the above manner, and giving gradually somewhat less than the amount calculated. The result can then be checked by another plasma bicarbonate determination. Or the bicarbonate can be given at the rate of 3 or 4 grams per hour, and stopped as soon as the urinary pH shows a rise when tested as described above in connection with the bicarbonate retention test.

(3) In avoiding the production of over-alkalinity in the sense of a high pH, it is essential to consider not only the amount of bicarbonate ad-

ministered, but also the *rate* at which it is permitted to enter the circulation. If the condition is, for example, the most familiar one of compensated alkali deficit (Area 6, Fig. II), the more important of the two factors, the pH, is still normal. It is desirable to restore also a normal bicarbonate of the body fluids in order to place a safe reserve of alkali between the existing condition and the distinctly dangerous one of uncompensated alkali deficit (Area 9, Fig. II). But the restoration of the alkali reserve should be accomplished so gradually that at no time is the pH harmfully shifted to over-alkalinity. If bicarbonate is administered *slowly,* the organism can, by retarding somewhat its respiration, retain sufficient carbonic acid so that $BHCO_3$ and H_2CO_3 make parallel increases, and the $BHCO_3 : H_2CO_3$ ratio and the pH remain normal.

If bicarbonate is given as prescribed by Stillman(*a*) (1919) for diabetic acidosis, at the rate of 3 grams per hour, dissolved in cold water and given by mouth, until the blood bicarbonate becomes normal, there appears to be little danger of causing an abnormally high pH. If, on the other hand, bicarbonate is injected intravenously in massive doses, a rise in the blood pH seems inevitable. Instances of tetany in both adults (Harrop(*a*), 1919) and in children (Howland and Marriott(*b*), 1918) as the result of intravenous injection of bicarbonate are on record. It occurs also after overdosage, even of alkali given slowly by mouth, but the danger seems distinctly less in this form of administration.

It appears that as a rule the most desirable way to administer bicarbonate is by mouth in doses of not over 0.1 gram per kilo body weight each hour. In uncompensated acidosis, with lowered pH and air hunger, this rate can perhaps be doubled. When, as in diarrhea of infants, the effect of bicarbonate on the alimentary canal would be unfavorable, intravenous injections must be used, but massive single doses are to be avoided in favor of smaller repeated doses. And finally, when by correcting the diet, as by use of a green vegetable diet or protein diet low in fats in diabetes (Stillman, 1919), or by glucose or lactose administration in non-diabetic ketoses (Duncan and Harding, 1918) the organism can be put into a position to restore its own acid-base balance, it appears desirable to assist it to do so without alkali administration.

Acidosis in Certain Conditions

Diabetes. *Type and Cause of Acidosis.*—The acidosis which occurs in severe diabetes is caused, as shown in the notable work of Magnus-Levy(*e*) (1899), by rapid formation of the so-called acetone-bodies, acetoacetic and β-hydroxybutyric acids, the products of incompletely burned fatty acids. Magnus-Levy found no evidence of significant formation of other

acids, nor did Van Slyke and Palmer (1920) in comparing the excretion of the acetone bodies with that of the total organic acids.

Diagnosis of Acidosis in Diabetes.—In diabetes acidosis may be excluded by a qualitative test for acetone bodies in the urine, since they appear never to markedly affect the internal acid-base balance, without appearing in the urine in sufficient amount to be readily recognized. If acetone bodies appear, however, it is impossible to tell, even when their concentration in the urine is maximal, whether they are causing alkali deficit or not, and one of the direct measures of the alkali reserve (blood $BHCO_3$ estimation or bicarbonate retention test) is required, with functional tests, alveolar CO_2 or the rate of acid plus ammonia excretion, as somewhat less accurate alternatives.

In determining the acid-base balance in the blood in diabetic acidosis, it appears that for ordinary diagnostic purposes, a bicarbonate determination without the pH is sufficient. Unless unusual complications are present the respiratory mechanism appears to be fairly normal, and the two conditions encountered are either compensated alkali deficit (Area 6, Fig. II) with low $BHCO_3$ and normal pH, or, in terminal coma, uncompensated alkali deficit. In the latter the pH is lowered, but the $BHCO_3$ is also greatly lowered.

Therapy.—The therapy in diabetic acidosis depends so entirely on the condition of the individual patient that an attempt to treat the condition according to a uniform rule would be unnecessarily disastrous in a considerable percentage of the cases so treated. A definite procedure for guiding the treatment by the plasma bicarbonate and the clinical condition of the patient has, however, been laid down on the basis of experience by Stillman (1919), and the reader is referred to his publication. The treatment in outline consists of a fast, with abundant fluids, accompanied, if the plasma bicarbonate CO_2 is below 30 volumes per cent, by bicarbonate given by mouth at the rate of 3 grams per hour. If the plasma bicarbonate falls during the fast, as occurs in occasional cases, a moderate diet consisting chiefly of protein (meat and eggs) is given, with a later resumption of fasting to render the patient aglycosuric. After the aglycosuric condition is obtained, the fast is broken by giving a gradually increasing diet of green vegetables. A logical basis for estimating the amount of fat, carbohydrate, and protein consumed in such proportions that ketone formation is avoided has recently been proposed by Shaffer (1921) and Woodyatt (1921).

Nephritis. *Type and Cause of Acidosis.*—That acid intoxication occurs in nephritis was shown by Jaksch(*f*)(1887). Straub and Schlayer (1912) have given evidence that acid intoxication is a cause of uremic coma, an explanation which is well supported by the fact that a patient in uremic coma can be brought out of it by bicarbonate injection. Chace

and Myers(*c*)(1920) have shown that lowered plasma bicarbonate occurs frequently in chronic nephritis, and consider it a grave prognostic sign.

The states of the acid-base balance that have been observed in nephritis are those of compensated alkali deficit (lowered blood bicarbonate with normal pH) finally developing during the premortal coma into uncompensated alkali deficit (very low bicarbonate and pH also lowered) (Peabody(*d*)(*e*), 1914). The lowest blood pH observed in man according to the writer's knowledge was one of 6.95 determined by Cullen in the hospital of the Rockefeller Institute in a nephritic shortly before death in uremic coma.

The cause of acidosis in nephritis has been generally assumed to be failure of the kidneys to excrete the acid products of normal metabolism. There is no formation of acetone bodies or the other known organic acids. Marriott and Howland(*a*)(1916) have found an increase in the plasma PO_4 of nephritics which indicates that retention of phosphoric acid may be partly responsible for the lowered alkaline reserve. In certain nephritics Henderson and Palmer (1915) found the ratio (titratable acid) : (ammonia) in the urine to be abnormally high. Marriott and Howland(*c*) (1918) have found a similar ratio after feeding acid phosphate, which is further evidence of the possibility of phosphoric acid retention in nephritic acidosis. That there may be in nephritis not only a retention of normal acid metabolites, but also a specific acceleration of acid formation is a possibility indicated by recent experimental work of Wallace (1921).

Diagnosis.—Combined blood bicarbonate and pH determination or the alkali retention test, appear necessary. The indirect methods are uncertain.

Therapy.—It is at present uncertain whether the moderate compensated alkali deficit of chronic nephritis is of importance in accelerating the progress of the disease. Whether a patient in such a condition is benefited by therapeutic measures to restore the alkali reserve has not yet been shown. Since the acid-base balance is obviously unstable, however, and the compensated acidosis may become uncompensated with accompanying coma and death, it may possibly be desirable, in nephritics with a tendency towards low blood bicarbonate, to assist the body in maintaining its alkali reserve by dietary means. Such would be a diet abundant in fruits and vegetables, which produce more alkali than acid when burned in the body, but sparing in meats and other protein foods, and in cereals, which produce more acid than alkali when metabolized.

In uremic coma the air-hunger can be alleviated and life prolonged, perhaps, for a few days by bicarbonate administration. Its effects on both clinical condition and acid-base balance are outlined in a description of a case by Means, Bock, and Woodwell (1921). Usually alkali therapy prolongs the life of a comatose nephritic only a few days; but in an instance observed by the writer (case of Dr. Edgar Stillman) such a

patient, with uncompensated acidosis, regained and held a normal acid-base balance after bicarbonate dosage, and is still alive some months later.

Diarrhea of Infants. *Type and Cause of Acidosis.*—The clinical condition which is frequently accompanied by alkali deficit is described by H. Schwarz (personal communication) as follows: "Half the cases occurred in children up to 6 months of age, the other half from the 6th to the 12th months. Temperature varies from subnormal to high. Heart rate is often rapid. Urine is diminished in quantity. The toxic symptoms consist of marked irritability, gradually subsiding into apathy, semi-coma, and coma. Some of the children present rapid shallow breathing, others the deep and labored breathing typical of diabetic coma."

Some of these cases described by Schwarz show high blood urea, others show lowered plasma bicarbonate, and a third group show both changes. Of 23 cases of toxic diarrhea, Schwarz found 7 with acidosis and urea retention, 4 with acidosis alone, 6 with urea retention alone, and 6 with blood figures normal for both bicarbonate and urea. The prognosis was bad for all.

Lowered plasma bicarbonate in such cases appears, as a rule at least, indicative of a genuine alkali deficit (Area 6, Fig. II), although perhaps in some cases (see observations of Schloss below) it may be secondary effect of hyperpnea due to an unknown respiratory stimulant (Area 2, 3, Fig. II).

Howland and Marriott(*a*)(1916) found associated with hyperpnea and low alveolar CO_2 abnormally large bicarbonate retention and decreased alkalinity of the blood by Sellard's test (color of concentrated alcoholic filtrate with phenolphthalein). These effects combined are explicable only by a genuine loss of buffer alkali from the body. Schloss and Harrington (1919) found lowered plasma bicarbonate and urine of high acidity (pH below 5.3) in similar cases. Rapid breathing and consequently lowered alveolar CO_2 sometimes occurred without bicarbonate deficit in the blood. Such cases were characterized by a urine of pH greater than 5.3. Schloss has more recently observed a small proportion of marasmic infants with low plasma bicarbonate and high urinary pH (personal communication). The condition in such cases is perhaps that indicated by Area 3, Fig. II, the fall in plasma $BHCO_3$ being a secondary effect of H_2CO_3 deficit caused primarily by prolonged hyperpnea.

Concerning the nature of the acids which cause the alkali deficit in these cases we have no knowledge. The acetone bodies appear to be excluded, since they appear irregularly, and in amounts too slight to account for marked changes in the acid-base balance.

Diagnosis.—The present data indicate that in the cases of the type described a diagnosis of acidosis may be made in most cases by a determination of the plasma bicarbonate, although it is possible that an erroneous positive diagnosis may occasionally be made unless the pH of the blood

or urine s also noted. If a low blood bicarbonate is due to genuine alkali deficit, the urinary pH will be, according to Schloss, below 5.3; if the fall in blood bicarbonate is merely a secondary result of hyperpnea, the urinary pH will be much higher. Because hyperpnea and in consequence low alveolar CO_2 may occur when the acid-base balance of the blood is normal, it appears that alveolar CO_2 figures are unreliable for the diagnosis.

Therapy.—Schloss and Harrington (1919) in cases with lowered plasma bicarbonate and acid urine give sodium bicarbonate intravenously until the urinary pH exceeds 5.3. Bicarbonate by mouth is contraindicated because of its effect on the alimentary tract.

Cyclic Vomiting of Children. *Type and Cause of Acidosis.*—This condition of unknown cause is, at times at least, accompanied by an exceedingly rapid formation of acetone bodies, and acid-intoxication as an important factor in the symptoms was recognized by Edsall(*a*)(1903). Studies on the acid-base balance of the blood appear as yet lacking. That the acidosis may temporarily approach in severity that of diabetic coma seems probable, however. The intense air-hunger, rapid pulse, and semi-comatose but excited condition typical of the precoma stage of diabetes are also noted here (Hecker, 1914; Hodges, 1914). In one case which chanced to come under the writer's observation the 24-hour excretion of ammonia plus titratable acid exceeded 100 c.c. of 0.1 *N* solution per kilo, which in diabetes indicates acidosis bordering on coma (Table II). The alkali retention was correspondingly high.

Diagnosis.—The cause of the disturbance in acid-base balance is, as in diabetes, the acetone bodies. Acidosis may therefore be detected or excluded by the same methods described above for diabetes.

Therapy.—Edsall (1903) introduced the use of bicarbonate. When it can be retained, bicarbonate given by mouth during an attack appears greatly to alleviate the air-hunger and other symptoms. Given when the onset is indicated by the prodromal symptoms and appearance of acetone bodies in the urine it may abort the attack. The general treatment is detailed by Hecker (1911) and by Marfan (1916).

Acidosis after Anesthesia.—The condition of the acid-base balance during and after anesthesia is at present so little understood that one does not appear justified in drawing conclusions in a given case unless both blood bicarbonate and pH are known. That a fall in bicarbonate occurs during etherization is certain (Caldwell and Cleveland, 1917). Henderson and Haggard(*b*)(1917), however, explain it as due to H_2CO_3 deficit from hyperpnea (Area 3, Fig. 2), and Henderson, Haggard, and Coburn (1920) recommend administration of air containing CO_2 as the remedy. Their explanation is diametrically opposed to the results of Menten and Crile (1915) and of Van Slyke, Austin, and Cullen (1920) who found lowered pH in etherized animals. Lowered pH combined with lowered bicarbonate indicates uncompensated acidosis. The observations of Collip

(1920) on etherized dogs also point to uncompensated acidosis. Reimann, Bloom, and Reimann (1921) were unable clinically to confirm Henderson, Haggard, and Coburn's favorable therapeutic results with CO_2 administration and believe that on the contrary bicarbonate should be given when the plasma CO_2 capacity, as determined by Van Slyke and Cullen (1917), falls below normal.

More clinical and experimental data are obviously required before definite conclusions can be drawn concerning the effects of anesthesia on the acid-base balance, or concerning the treatment indicated.

Metabolism in Fever and in Certain Infections . . . . . *Eugene F. Du Bois*

Metabolism in Fever—Introduction—Metabolism in Typhoid Fever—The Total Metabolism in Typhoid Fever—Direct and Indirect Calorimetry—The Regulation of the Body Temperature—Surface Temperature—Water Metabolism—The Respiratory Quotient—Carbohydrate Metabolism—Fat Metabolism—Protein Metabolism—The Effect of Food in Typhoid Fever—Specific Dynamic Action of Food in Typhoid Fever—Body Weight—Urinary Constituents—Van't Hoff's Law and the Basal Metabolism in Fever—Metabolism in Lobar Pneumonia—Basal Metabolism—Nitrogen Excretion—Chlorid Metabolism—Blood Constituents—Acidosis in Pneumonia—Miscellaneous Metabolites—Metabolism in Tuberculosis—Total Metabolism—Character of Foodstuffs Oxidized—Sputum—The Effect of Food—Temperature Regulation in Tuberculosis—Blood Constituents—Erysipelas—Total Metabolism—Metabolism in Malarial Fever—Total Metabolism—Temperature Regulation in Malaria—Character of Foodstuffs Oxidized—Direct and Indirect Calorimetry—Chlorids and Phosphates in Malaria—Fever Caused by the Parenteral Injection of Foreign Proteins—Cholera—Miscellaneous Infectious Diseases of Men—Experimental Fever in Animals.

Metabolism in Fever and in Certain Infections

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NEW YORK

Metabolism in Fever

Introduction

Recent advances in technic have directed the attention of all who are interested in the study of metabolism towards the respiratory exchanges, the chemistry of the blood and the function of the kidneys. As a result of this there have been great advances in our knowledge of the pathological physiology of fever. The picture which is now presented is much more comprehensive than it was a few years ago, and somewhat simpler, because modern research has removed many false theories which were based on incorrect data. Fortunately we are no longer dependent on the results of animal experimentation, since most of the methods of investigation have been successfully applied in the clinic. This is a great step in advance because there is no comparison between the relative value of results obtained on laboratory animals with artificial fevers and similar results on men with the common infectious diseases.

It has seemed advisable in this review of the metabolism in fever to lay the chief emphasis on the findings of those who have worked with human subjects. The older experiments with animals have been well reviewed in the literature and have performed their function in showing the way to clinical investigators. In similar fashion the older experiments on man have been discussed so often and so well that most of them may be omitted and attention directed to more recent workers who have repeated the investigations. The latter may not have changed the general conclusions to any great extent but they have, as a rule, used better methods and proved their points more conclusively than the pioneers.

The usual method of exposition of the subject has been to show one phase of metabolism in all the various infections and hyperthermias of man and the lower animals before passing on to the next subject. For

instance, the nitrogen elimination is discussed in typhoid fever, pneumonia, "heat puncture," etc. This method has great advantages but it has seemed advisable to try a new method of approach and take up the various important diseases one by one. The first disease so treated is typhoid fever and the disturbances of metabolism which occur in this infection will be presented as fully as possible. If one such disease is well understood all other fevers can be treated much more briefly and emphasis laid only on the points in which they differ from typhoid.

Among the earlier reviews of the subject of fever we find that of Liebermeister(*b*), who brought forward the conception that temperature regulation was merely adjusted at a higher level than normal. Senator(*b*) emphasized the relative preponderance of protein in the metabolism in fever during the years between 1873 and 1911. Wood, in Philadelphia, showed the increased metabolism in fever by means of a calorimeter. In more recent times we have the comprehensive work on the metabolism of tuberculosis by A. Ott, and the discussion of the dietetic therapy of fever by von Leyden and Klemperer(*a*). Garratt, in 1903, added an excellent review of the literature to his own studies on the organic and inorganic constituents of the urine in fever. Kraus, in von Noorden's system of metabolism, covered the whole subject of fever and infection with a careful discussion of the results of work on animals. MacCallum, two years later, wrote from very much the same viewpoint. The physiology of body heat has been discussed in a classical manner by Tigerstedt(*b*) in 1909. Isaac Ott(*b*), of Philadelphia, one of the pioneer workers in the subject of heat puncture, has published a little book on fever with a summary of the literature. The most comprehensive discussion is that of P. F. Richter(*e*) in Oppenheimer's "Handbuch der Biochemie." He reviews the subject from the critical viewpoint of practical clinician who has done a large amount of personal experimentation on animals and man, and has had the benefit of long association with one of the pioneers of fever investigation, Senator. This article has never received the attention it deserves, but it will repay the reader not only in its subject matter but also as a study of an excellent mode of treatment of a difficult review. Hewlett, in his book on the functional pathology of internal diseases, has reviewed the whole question of heat regulation and given the important references up to 1913. Lusk(*e*), in his well-known text book on nutrition, has treated the changes in metabolism in fever from the standpoint of the physiologist and biochemist.

Metabolism in Typhoid Fever

It is not surprising that more work has been done on the metabolism in typhoid fever than in any other infection. The disease has been prevalent and even at the present date can be found in most of the large

clinics at some time during the course of the year. The fever itself is fairly regular in its course and offers a period of rising temperature, a period of level temperature, sometimes two weeks long and a period of falling temperature with wide remissions. Patients with this disease lend themselves well to experimental procedures. They are apathetic and are not worried by the display of apparatus. Their circulatory systems are dependable and cause the investigator little anxiety.

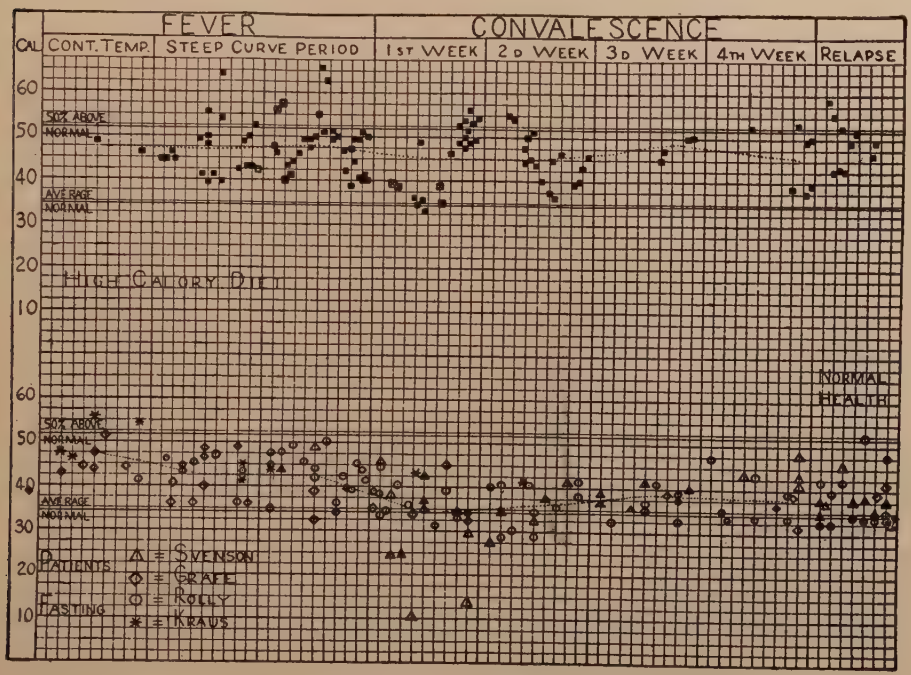

Fig. 1. The total metabolism of patients with typhoid fever expressed in terms of calories per square meter (Meeh's formula) per hour. Lines are drawn to show the average normal and the point 50 per cent above the average normal. The upper part of the figure gives the results obtained by Coleman and Du Bois on patients on the high calory diet, the lower part shows the cases on low diets studied 14 or more hours after the last meal by Kraus, Svenson, Grafe and Rolly.

Although typhoid fever may be mild in its course the majority of cases are severe enough to cause great prostration, and these severe cases are so greatly influenced by treatment that they may be divided into two groups which differ from each other as much as if they were two different diseases. In the first group we have the patients who are kept on the old-fashioned semi-starvation diet of broths, lemonades with egg albumin and milk in limited amounts. These show the classical picture of the so-called "typhoid state" with emaciation, delirium, tremors, etc. In the second group are the patients who are given liberal diets of more than two thousand calories a day. These show but slight emaciation and

suffer so little from nervous symptoms that they read the newspaper every day. This is the real picture of typhoid fever, the other is a combination of typhoid and inanition.

The Total Metabolism in Typhoid Fever.—The literature dealing with the respiratory metabolism in typhoid fever is voluminous. Much of it is bedevilled by poor technic and it will be a long time before science can exorcise the numerous wild theories which were manufactured to explain false data. Fortunately at the present time we have consistent reports from many clinics and the facts are well established.

The total heat production and the destruction of protein during the febrile period are increased but otherwise the metabolism is much the same as in normal subjects. There is no evidence of any profound disturbance in the combustion of fats or carbohydrates. Even the increase in total metabolism is comparatively slight, not approaching the levels found in severe hyperthyroidism or moderate muscular exercise. The data obtained by Kraus(*a*), Svenson, Grafe, Rolly, and Coleman and Du Bois(*a*) (1914) have been summarized in Figure 1 and Table 1. All of these investigators used the method of indirect calorimetry, determining the consumption of oxygen and production of carbon dioxid. Grafe, with a respiration chamber, used experimental periods several hours long. All the others used periods of 10 to 30 minutes. The patients lay quietly in bed, attached by masks, nose-pieces or mouth-pieces to some type of apparatus which made it possible to analyze the expired air. Kraus, Grafe and Rolly studied patients on low diets which did not cover the caloric requirements and made their observations in the morning 12 to 14 hours after the last meal. Svenson used similar subjects during convalescence. Coleman and Du Bois, in their first series, gave their subjects 35 to 102 calories per kilogram per diem and measured the metabolism during the

Table 1. Heat Production During the Course of Typhoid Fever

Period	Percentage Increase above Average Normal			
	High calory patients after recent meal	Low calory patients fasting	Calorimeter series. Adults	Relapse
Ascending temperature	..	..	30	25
Continued temperature	37	38	44	51
Early steep curve	36	23	24	36
Late steep curve	40	24	27	16
Convalescence, first week	32	—1	0	
Second week	31	4	5	
Third week	40	12	17	
Fourth week	33	11	5	
Fifth week	..	..	4	

afternoon a few hours subsequent to the last meal. In their second series they gave similar diets but determined the metabolism in the morning, 12 to 14 hours after the last meal. These patients were observed for three-hour periods in the respiration calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital. At the time this work was published the results were compared with a normal standard of 34.7 calories per square meter per hour according to Meeh's surface area formula. Although there are certain inaccuracies in this formula it is the best available for this typhoid series and probably does not introduce an error as great as five per cent for the adults. In recent years, however, we have realized that the metabolism is high during adolescence, and this makes it necessary to recalculate their results. In Table 1 only the adult cases are used for the averages. If we compare the averages for the three boys of 12 to 18 years of age with the proper standards we obtain the following results: Ascending temperature period +9 per cent; continued temperature +2 per cent; early steep curve +11 per cent; late steep curve +3 per cent; convalescence first week —23 per cent, second week —17 per cent.

The analysis of these figures for adults and children brings out many points of interest. It is somewhat surprising to find that the average increase during the periods when typhoid patients show great toxemia is only 23 to 44 per cent. In typhoid fever the young subjects produce about the same number of calories per unit of surface area as the adults with the disease of the same severity. Just why the metabolism of the boys should not be higher than that of adults is not easy to understand. Allen and Du Bois have called attention to the fact that the diabetic children reported by Benedict and Joslin showed low metabolism and have suggested that the normal stimulus of the growing organism is checked by diabetes. This may be true of fever but it is quite possible that the stimulus of growth takes the place of the stimulus of fever and that there is no more summation than we find in the case of the specific dynamic action of food in fever.

Table 1 shows that there is a striking similarity in the results obtained during the febrile periods in the three groups of typhoid patients. It seems to make little difference whether the patients are on low diets or high diets or whether they are fasting or digesting a recent meal. Normal subjects on low diets after a period of a couple of weeks would exhibit a lowered heat production. Normals studied a few hours after a hearty meal have a distinctly increased metabolism. In typhoid fever the food does not cause any significant rise in energy consumption. The reasons for this will be discussed under the heading of specific dynamic action. The practical application of this is that we need not be afraid of increasing the fever by giving food.

Coleman and Du Bois have estimated the total metabolism of their typhoid patients studied in the calorimeter by adding to the basal figures 10 per cent for muscular activity and 3 per cent for the specific dynamic action of food. During the febrile periods the estimates fall between 1,700 and 2,600 calories per day, and these figures may be considered a fair average for the general run of typhoid patients. If we want to make an exact estimate in any individual case it is necessary to determine his respiratory exchanges but we can probably come within 5 to 20 per cent by the following process: First determine the surface area and multiply by the normal figure for a person of that age and sex. This will give his normal basal calories. Next add the percentage increase caused by the particular period of the disease as shown in Table 1 and add a suitable percentage to cover the muscular activity. This latter will range from 10 per cent for a quiet subject to 50 per cent for a man who is delirious. There are little exact data on the effect of restlessness on the heat production in fever, but in a few cases which have been observed while delirious the figures are not much higher than similar patients at rest.

Direct and Indirect Calorimetry.—Before it was possible to study fever patients in a respiration calorimeter a number of investigators were inclined to believe that there was some abnormal process of metabolism in disease which interfered with the proper oxidation of proteins, fats or carbohydrates in such a manner that there was an error in the method of calculating the heat production from the respiratory exchanges. This point was raised by those who obtained bizarre results through unsuspected errors in technic. Rather than admit that anything could be wrong with the experiments they attacked the validity of the ordinary laws of metabolism and even the law of the conservation of energy.

Fortunately the calorimeter has been able to prove that there is no such profound qualitative change in the metabolism in fever. It has measured the heat production by the method of direct calorimetry which determines by physical means the calories of radiation, conduction, vaporization and the storage of heat in the body. At the same time it measures the heat production by the method of indirect calorimetry which uses chemical methods to determine the grams of protein, fat and carbohydrate oxidized and calculates the calories by using the standard heat values for these food-stuffs. Coleman and Du Bois in typhoid fever and convalescence measured in all experiments by the direct method 12,540 calories, by the indirect method 12,822 calories, a difference of only 2.2 per cent. In the febrile experiments, excluding the first periods the direct method gave 5,584 calories, the indirect 5,720. These differences are as small as can be expected when experimental periods of only three

or four hours are used. The amount of heat stored in the body cannot be determined exactly by means of the rectal temperature in short periods since no one spot in the body gives an accurate index of the temperature change of the whole body. In few diseases has the agreement between the direct and indirect methods been closer than the above, and although it is impossible by this method to rule out minor changes in the metabolism we can say that there is no reason to suspect any profound change in the oxidative processes or any interference with the law of the conservation of energy.

The Regulation of the Body Temperature.—Attempts have been made to determine the mechanism of temperature regulation by means of indirect calorimetry. If we know the amount of heat produced in the body and assume that the changes in the rectal temperature indicate the changes in the average temperature of the whole body we can calculate the heat elimination during the experimental period. Each kilogram of body is equivalent to about 0.83 liter of water in its power to store heat. A man weighing 70 kg. has the hydrothermal equivalent of about 58.1, and if the temperature rises one degree C. it means that 58.1 calories have been stored in the body, if it falls one degree the same amount has been lost. In the long run this method gives fairly good results, but as we shall see later it is not always satisfactory to assume that a single thermometer placed in the mouth or rectum indicates with sufficient rapidity the changes in the extremities or in the large proportion of the whole mass which lies just beneath the skin. Barr and Du Bois have calculated that in a man who weighs 70 kg. about 15 kg. is within 1 cm. of the surface.

The respiration calorimeter which measures both heat production by chemical methods and heat elimination by physical methods furnishes an exact means of determining how the body temperature is raised or lowered in fever. Isaac Ott(*a*), of Philadelphia, in 1892, and Likatscheff and Avroroff, of Petrograd, in 1902, measured the heat elimination of malaria patients in calorimeters but did not use for their calculations the method of indirect calorimetry. Coleman and Du Bois, using both methods, published diagrams showing the relationship of heat production and elimination in all the experiments where the methods of direct and indirect calorimetry agreed within 5 per cent. In these experiments the small difference between the two meant that the rectal temperature curve was close to that of the average body temperature. After several years' work with many diseases had shown the accuracy of the Sage calorimeter Barr originated another method of calculation which permits us to obtain much valuable information from the typhoid experiments previously discarded, namely those in which the direct and indirect methods differed by more than 5 per cent.

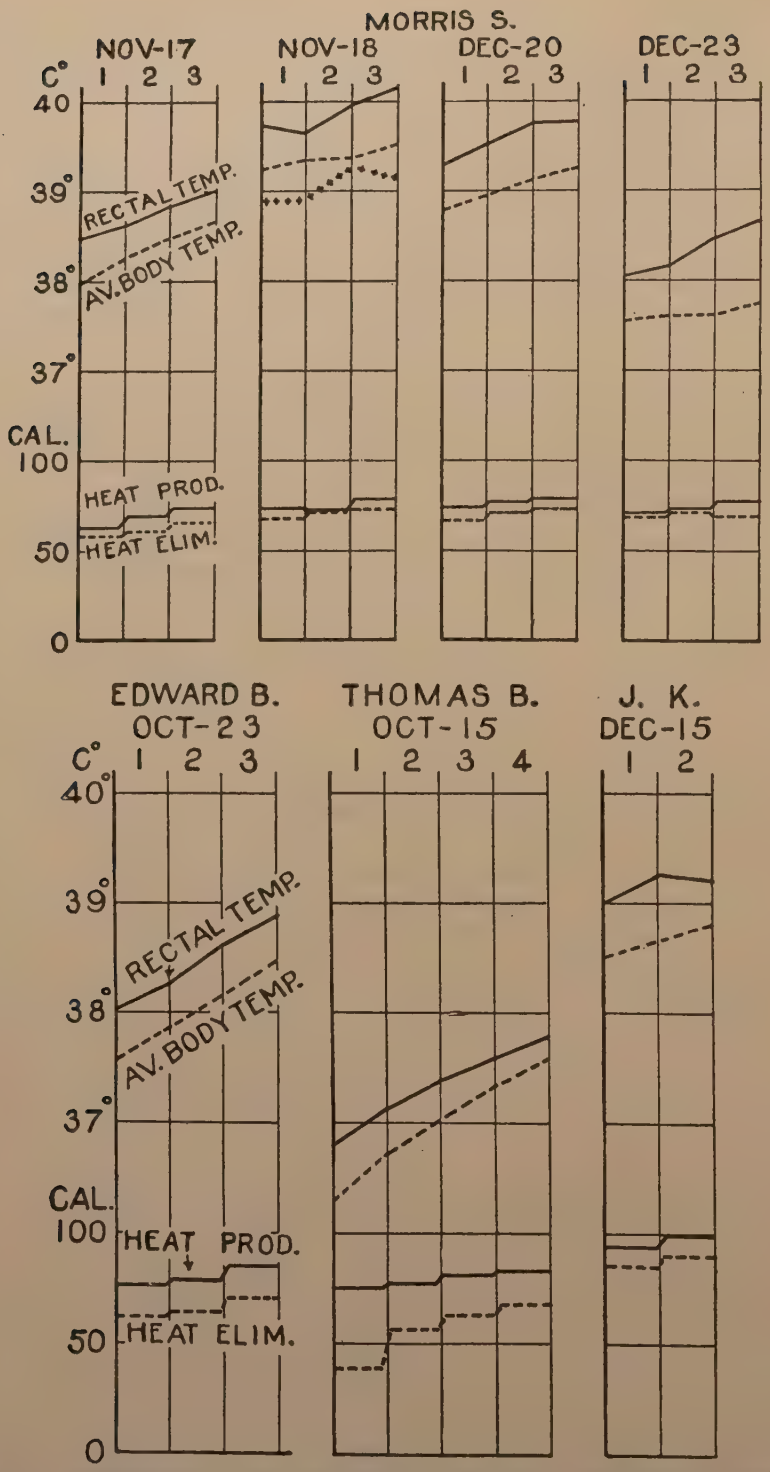

Fig. 2. Experiments on typhoid patients with rising temperature showing an increasing heat production which outweighs the increasing heat elimination. The uppermost continued line shows the rectal temperature, the dash line the average body temperature changes. This latter line is arbitrarily started one-half degree below the rectal line. The line of crosses gives the "surface" temperature in a few experiments. The lower continued line shows the heat production in hourly periods, the dotted line the heat elimination.

This calculation is fairly simple. The difference in calories between heat production and heat elimination is divided by the hydrothermal equivalent of the body and the resultant is the average body temperature change expressed in degrees centigrade. If, for instance, during a certain experimental period the heat production was 100 calories and the elimination 60 it would mean the storage of 40 calories in the body. If the subject weighed 70 kg. his hydrothermal equivalent was 58.1 liters of water. 40 divided by 58.1 gives 0.68, the degrees C. that the average body tem-

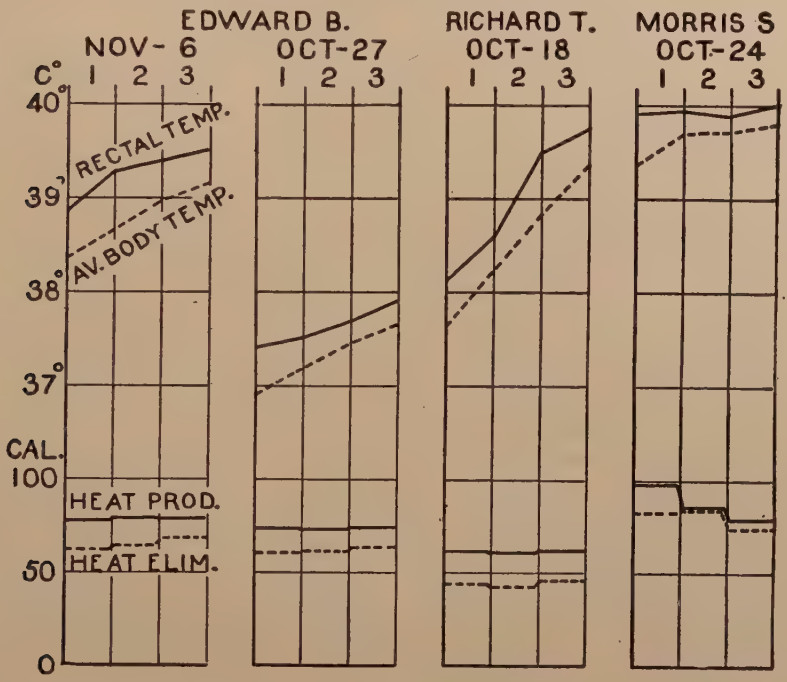

Fig. 3. Typhoid patients with rising temperature, heat production remaining almost constant and in one case falling.

perature must have risen during the expirement. Results have frequently indicated that although the rectal temperature usually shows about the same change as the average body temperature there are times when the two differ in extent and even in direction.

Diagrams have been made showing the heat production and changes in the rectal and average body temperatures of the typhoid patients studied in the calorimeter. (Figs. 2 to 5.)

No better opportunity of studying this subject has been afforded, and it seems desirable to devote some space to the analysis of these charts. Most of the patients show a rising temperature because they were studied in the morning and early afternoon. As was pointed out in the original

communication the rising temperature is usually accompanied by an increasing heat production which outweighs the increasing heat elimination. (Fig. 2.)

In some cases in spite of a rising temperature the heat production remains constant, having established itself at a level considerably above that of the heat elimination. (Fig. 3.) In one notable exception (Fig. 3, Morris S., Oct. 24), there is a rapid decrease in heat production during the second and third hours when the average body temperature is rising and the rectal temperature seems to have reached its zenith.

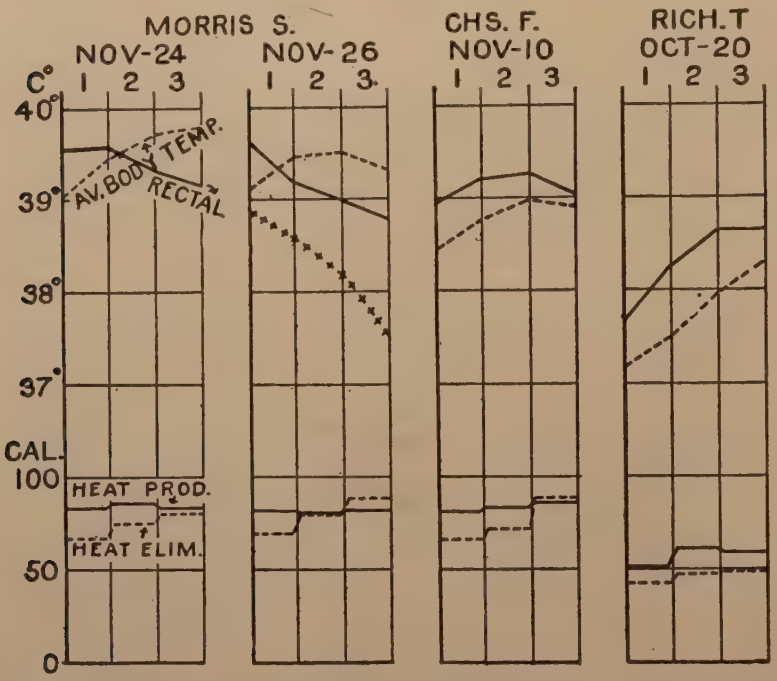

Fig. 4. Typhoid patients showing differences in the change in the rectal temperature and the average body temperature.

In most cases the rectal temperature and average body temperature rise at about the same rate but several experiments show that the rectal curve may fall while the body is still growing warmer. (Fig. 4.)

At the time when the temperature approaches its peak the skin and extremities are becoming warmer until they almost attain the heat of the internal organs. With the skin flushed and the arterioles dilated the blood begins to cool off the internal organs until they approach the temperature of the cooling surface.

The fall in temperature is caused by a rapidly increasing heat elimina-

tion due chiefly to increased vaporization of water from the skin. (Fig. 5.) The heat production diminishes, perhaps because of a change in the chemical regulation or because the metabolism is lower at lower temperatures or because there is some abatement in the toxemia which causes the fever.

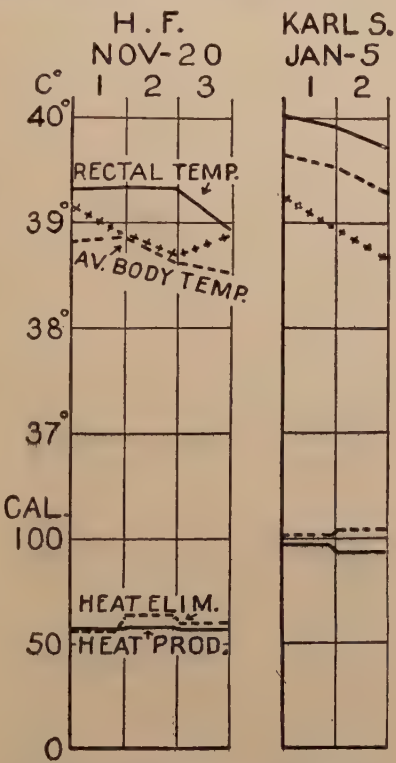

Fig. 5. Typhoid patients with falling temperature and rising heat elimination.

Surface Temperature. — Unfortunately we have little data concerning the temperature of any parts of the body except the mouth and rectum. Coleman and Du Bois in most of their typhoid experiments applied electrical thermometers to the skin of the thorax, one unit over the apex of the heart and the other over the dome of the liver. These were covered with pads of cotton so that they did not measure the actual skin temperature as influenced by evaporation but gave readings which probably approximated those of the subcutaneous tissue. They found that these surface thermometers indicated the changes in the average body temperatures slightly better than the rectal thermometer, but their readings were uncertain on account of the difficulty of keeping them in sufficiently close contact with the skin. If we look over their results in 34 experiments in the light of the new method of determining the average body change we observe the following:

Average Divergence of Change in Temperature of Rectum and of Surface of Thorax from Temperature of Body as a Whole.

Divergence of Rectal from Average Body Temperature	.....	5.0 per cent
" " Surface " " " "	.....	4.9 " "
" " Rectal from Surface "	.....	3.5 " "

We must remember that the "surface" thermometers were applied over the heart and liver, and they may have been greatly influenced by these two important viscera. They gave readings about one degree centigrade below that of the rectum and the individual experiments as well as the table of averages show that the surface and rectal curves agreed with each other more closely than either agreed with the changes in the average body temperature. This leads us to believe that the discrepancies between

direct and indirect calorimetry are due to unrecorded calories gained or lost in the arms and legs. Every clinician knows that the extremities may be relatively cold in fever patients. The whole subject of temperature changes in various parts of the human body needs further investigation.

Water Metabolism.—The typhoid patients studied by Coleman and Du Bois voided daily between 600 and 2,400 c.c. urine, averaging about 1,500 c.c. At the same time they excreted daily through skin and lungs about 700 grams of water. In some cases they lost more through skin and lungs than through the kidneys; for instance, Morris S., on November 26th, voided 780 c.c. in 24 hrs. and vaporized 105 c.c. during three hours in the calorimeter, which is at the rate of 840 c.c. for the day. Soderstrom and Du Bois compared all the patients studied in the Sage Calorimeter whose water elimination could be determined accurately and found that normal men under the standard conditions vaporized from skin and lungs an average of 29 grams an hour, losing in this manner 24 per cent of the total heat produced. Typhoid patients with rising temperature lose 22 per cent, typhoids with falling temperature 28 per cent, and in convalescence 21 per cent. Many febrile patients eliminated over 35 grams per hour but the ventilation system of the calorimeter was not able to remove the water vapor as fast as it was formed and the humidity of the chamber increased until it was higher than the standard conditions under which the normals were studied. Since the calorimeter can take care of the water vaporized by a normal man at rest this in itself shows that the vaporization is increased in typhoid fever. It is doubtful if the percentage of heat lost through vaporization is increased except when the temperature falls.

There is little evidence that the power of the kidneys to eliminate water is diminished in typhoid fever. Visible edema is rarely encountered and the invisible edema that is said to accompany high carbohydrate diets cannot amount to more than a few kilograms of retention.

Clinicians who estimate a water balance in a patient record under "Intake" only the fluids of the diet and under "Output" only the urine. In normal people the so-called solid foods furnish large amounts of water not only through their percentage content of water but also through the water formed from the oxidation of the carbohydrate, fat and protein. For all practical purposes we are close enough in our calculations if we estimate that 100 grams of solid food furnishes 100 grams of water to the organism. In fever this source of water is greatly diminished so the patient must be given fluids to compensate this loss in addition to the extra amount needed to balance the increased elimination through skin and lungs.

The Respiratory Quotient.—The respiratory quotient obtained by dividing the volume of CO_2 produced by the volume of O_2 consumed gives us valuable information regarding the character of the food-stuffs being metabolized in the body. If we know the excretion of nitrogen in the urine

during the period in which the respiratory quotient is determined we can, by the method of indirect calorimetry, estimate the grams of carbohydrate, fat and protein consumed and the percentage of total calories furnished by each. The following table gives some of the standard quotients:

TABLE 2.—STANDARD RESPIRATORY QUOTIENTS

	Respiratory Quotient
Carbohydrate	1.00
Fat	.71
Protein	.80
Av. normal subject 14 hrs. after last meal	.82
Starvation	.72
Total diabetes	.69
Carb. being converted into fat	1.00 — 1.39 +

We have at our command a large amount of data regarding the respiratory quotient in typhoid fever as determined by the investigators already quoted in regard to the total metabolism. Their findings are shown in Figures 6 and 7 and Table 3.

TABLE 3.—RESPIRATORY QUOTIENTS IN TYPHOID FEVER

Period of Typhoid	Low Cal. Diet 14 Hrs. After Last Food	High Cal. Diet 3-4 Hrs. After Last Food	Calorimeter Subjects	Calorimeter Subjects Relapse
Ascending Temp.	..	..	.79	.82
Continued Temp.	.78	.83	.77	.76
Early Steep Curve	.76	.87	.82	.78
Late Steep Curve	.76	.88	.82	.79
Convalescence				
First Week	.82	.93	.91	
Second "	.84	1.01	.88	
Third "	.92	.95	.81	
4th & 5th Weeks	.96	.91	.83	

Inspection of Figures 6 and 7 shows a few quotients slightly below the starvation level of .72, but these were all obtained with apparatus to which the patients were connected by means of mouth or nose pieces. With this technique errors of a few points are not infrequent. No quotients below .72 were found in the calorimeter and only one by Grafe, who used a respiration chamber. During the fever most of the quotients were between the level found in normal subjects and in starving men. The patients on a high calory diet studied shortly after their midday meals gave results almost as high as we should expect in normal subjects.

In convalescence we are at once struck by the number of abnormally high quotients, indicating that the subjects were deriving a large proportion of their calories from carbohydrates and in many instances were

even manufacturing fat from carbohydrate fourteen or more hours after the last meal. In the low calory cases the highest quotients were found in the fourth week of convalescence, in the high calory cases in the second week.

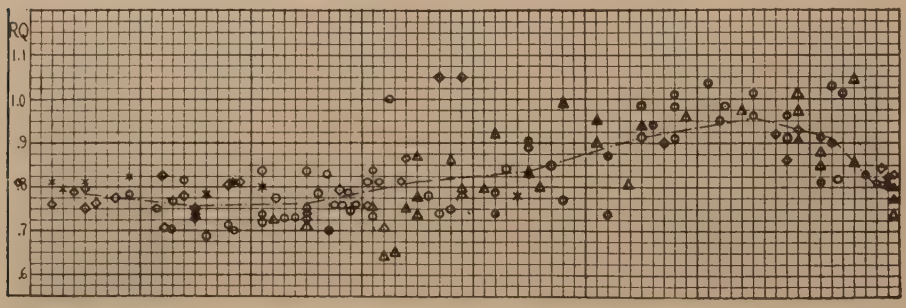

Fig. 6. The respiratory quotients of typhoid patients on low diets examined by Kraus, Svenson, Grafe and Rolly from 12-14 hours after the taking of food. Fig. 6 corresponds to Fig. 1.

It may be well to mention the fact that several observers have obtained quotients in typhoid fever which depart so far from the normal that we are forced to believe that there was something wrong with the technic. In fact, some of the experimenters on repeating their work with better apparatus have discovered their own errors. The concordance of all the

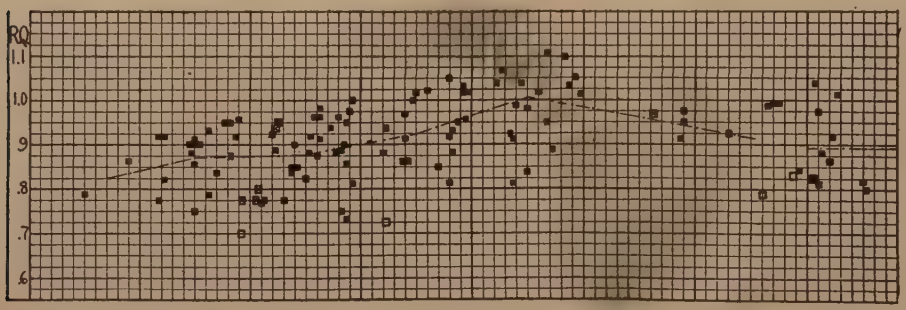

Fig. 7. The respiratory quotients of typhoid patients on the high calory diet. Solid squares indicate observations made shortly after meals; open squares, fasting observations; crossed squares, observations made from five to seven hours after the last meal or shortly after a light meal. Fig. 7 corresponds to Fig. 1.

recent studies has discredited this older work, which, however, is still found in the literature.

The modern work gives us a picture which can readily be explained. In the early stages of fever the patients who are on low diets rapidly approach the condition of partial starvation, exhausting, more or less completely, their stores of glycogen. For instance, Morris S., on October 24th, with a quotient of .76, was deriving 12 per cent of his calories from carbohydrate, 60 per cent from fat and 28 per cent from protein. Patients

who receive less food show quotients which indicate a degree of starvation as complete as that found in professional fasters three or four days after their last food. Patients who are well fed seem to differ in no way from normals, but there is evidence to indicate that they must be given more food than a normal man to bring the quotients to the same level. We must not forget that the pathologically high metabolism of protein has but little effect on the respiratory quotient.

In convalescence from typhoid the body rapidly replenishes its glycogen deposits if these have been depleted and perhaps is able to store larger amounts than normal. The quotients rise to an extraordinary level and the metabolism which was on a protein-fat basis in fever appears to be on a protein-carbohydrate basis. For instance Howard F., on December 6th, 14 hours after his last meal, had a quotient of 0.96, indicating that he was deriving 14 per cent of his calories from protein, 6 per cent from fat and 80 per cent from carbohydrate. The reason for this becomes apparent when we note that he received 1,380 carbohydrate calories on the previous day and find that the calorimeter indicated that his total requirement for the 24 hours was only 1,320 calories. If a convalescent with the characteristic enormous appetite consumes more carbohydrate than he can possibly oxidize it is not surprising that he should be converting some of it into fat many hours after the last meal. We should like to know if this occurs after long periods of starvation, either complete or partial, in normal men. The phenomena of the recovery from starvation have been strangely neglected.

Carbohydrate Metabolism.—The subject of the oxidation of carbohydrates has been covered in the paragraphs which discuss the respiratory quotient. There is no evidence of anything abnormal either quantitatively or qualitatively. Occasionally a slight glycosuria develops during typhoid fever. One such case, Frank W., was studied by Coleman and Du Bois. On the 18th day of his disease he excreted 32 grams of sugar, but his respiratory quotient was .86 and he derived 47 per cent of his calories from carbohydrate. This proved that the glycosuria was not of a diabetic type, and indeed the patient never showed glycosuria after leaving the hospital, although the urine was examined repeatedly during the course of the next few years. Such temporary appearances of sugar in the urine are probably due to the somewhat increased level of blood glucose which has been found in typhoid and other fevers by Hollinger, Rolly and Oppermann, Freund and Marchand and others.

The question of the rate of oxidation of ingested carbohydrates will be discussed under the heading of the effect of foods in fever.

Fat Metabolism.—We have seen that patients who are given small amounts of food derive a large proportion of their calories from body fat, just as in the case of a starving man or a diabetic. In typhoid, however, the destruction of protein is greater than in either of the other two condi-

tions. Senator has pointed out that the body becomes relatively poorer in protein and richer in fat but the absolute loss of both is so extensive that relative changes are comparatively unimportant.

There seems to be little or no acidosis in typhoid fever. Ewing and Wolf, who studied toxic patients on low diets, found that the ammonia excretion seldom exceeds the normal figures that would be expected with

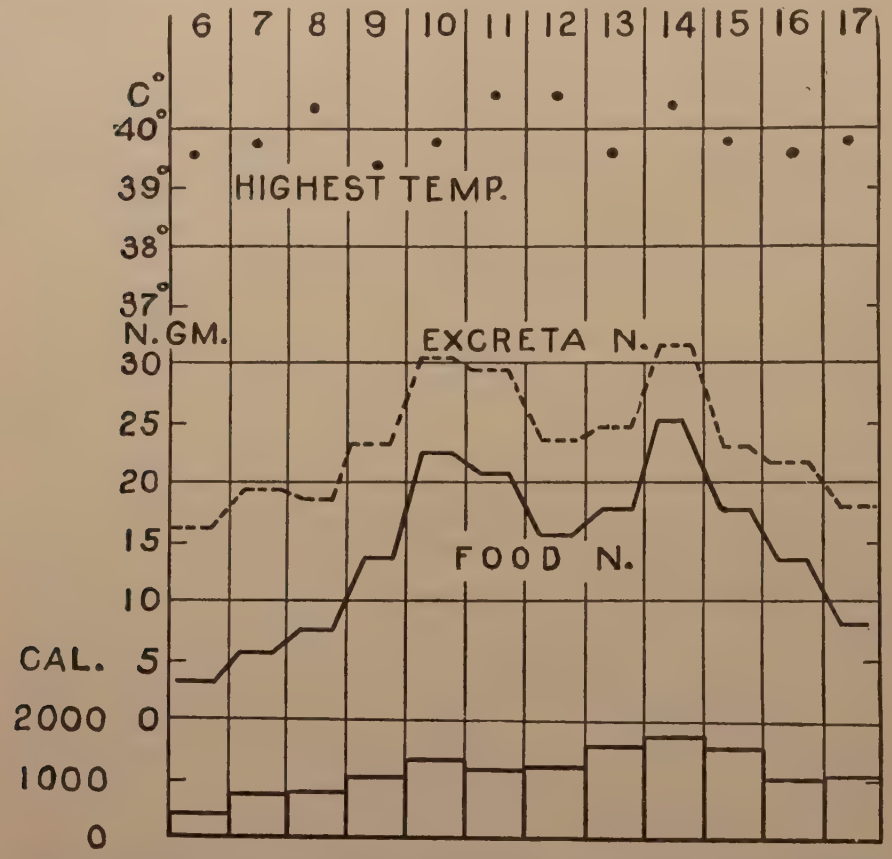

Fig. 8. Typhoid patient C. B., studied by von Leyden and Klemperer. Although the nitrogen of the food was increased to a high level the negative nitrogen balance persisted.

subjects who excreted a total of 15 to 25 grams of nitrogen daily. In one of their fatal cases the ammonia ratio reached 8.9 per cent and the output for the day was 2.09 grams. They suggest that the relative lack of acidosis may arise from the pronounced tendency towards the consumption of proteins. We can calculate that a nitrogen output of 25 grams shows that 81 grams of glucose has been derived from the carbohydrate forming portions of the protein molecule. Benedict's starving man derived only one-third as much from this source. We must remember

also that practically all typhoid patients are given some carbohydrates in their food.

Coleman and Shaffer, who studied patients on high calory diets, found the ammonia excretion was somewhat increased during the active stages of the disease but was not affected by the intake of carbohydrates. They

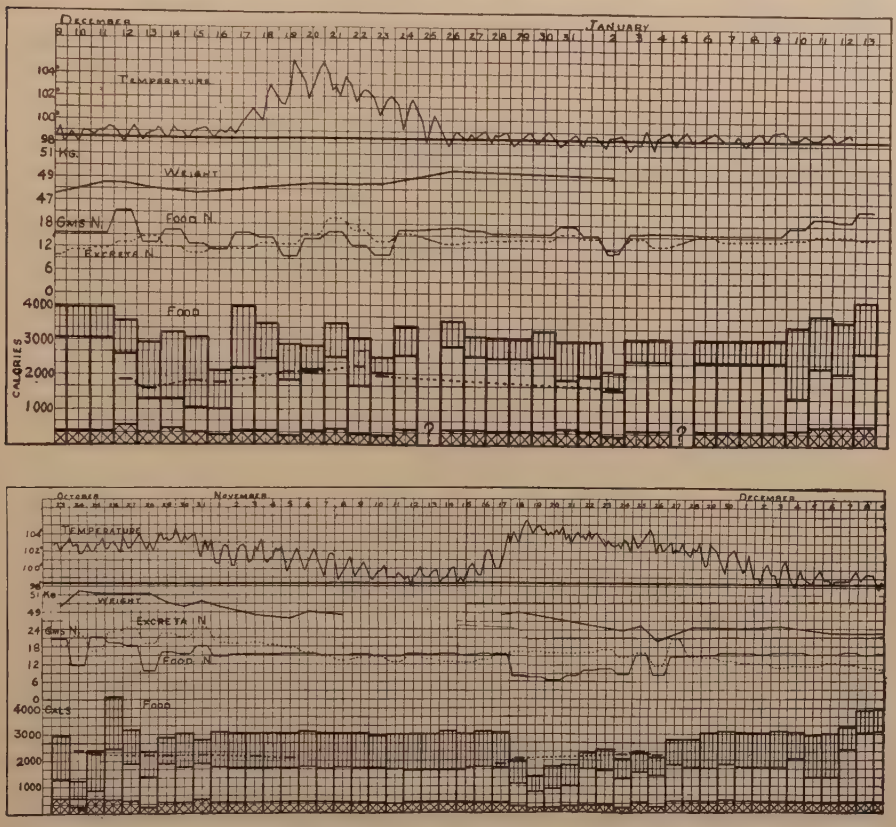

Fig. 9. Morris S.—Temperature, body weight. Food nitrogen, continuous line; excreta nitrogen, dotted line. At the base of the chart, columns representing total calories of food. Protein calories, crossed diagonals—fat calories, blank—carbohydrate calories, vertical lines. The dot-dash line represents the estimated heat production in calories for twenty-four hours. The dashes are placed on days of the observations in the calorimeter. Note that the calories of the food exceed the estimated heat production except for a period during the first relapse. Food was not measured on December 25th and January 5th. (Coleman and Du Bois, 1915.)

considered that this was probably coincident with an increased excretion of organic acids but never found diacetic or beta-oxybutyric acid even when the carbohydrates of the ration were low.

Increased acetone has been found by von Jaksch(*c*) and beta-oxybutyric acid by von Noorden(*c*).

Protein Metabolism.—Over sixty years ago it was clearly demonstrated that protein metabolism was increased in febrile diseases and many ob-

servers have since confirmed the fact that the nitrogen elimination is much higher than the intake. This is well demonstrated in the case of C. B., published by von Leyden and Klemperer(*b*) and by the cases Morris S. and Karl S. studied by Coleman and Du Bois(*b*). The results in these three cases are shown graphically in Figures 8, 9 and 10. C. B. was excreting about 18 grams of nitrogen daily on an intake of 3 to 7 grams during the first three days of the experiment, Karl S. was excreting 21 to 24 grams on an intake of 5 to 13 grams during his first four days. In some cases the

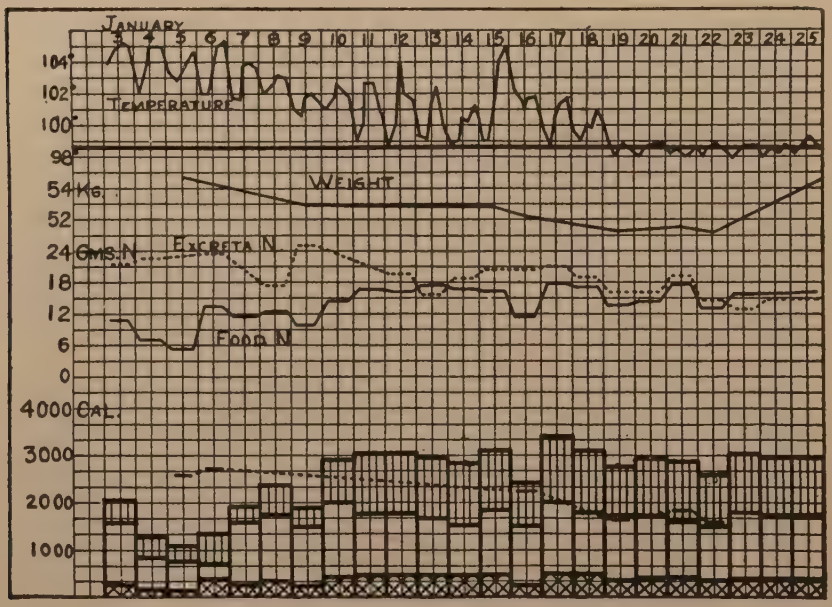

Fig. 10. Karl S.—Temperature and body weight. Food nitrogen, continuous line; excreta nitrogen, dotted line. The columns at base represent calories in food. Protein calories crossed diagonals, fat calories blank, carbohydrate calories vertical lines. Dot-dash line represents the estimated heat production in calories for twenty-four hours, dashes being placed on the days of the calorimeter observations. Note the negative balance during the last days of the fever when the patient was receiving in food more calories than the estimated heat production. (Coleman and Du Bois, 1915.)

nitrogen elimination rises 5 to 10 grams higher than the above figures. The negative nitrogen balance persists until the patient is able to take an amount of food which has a caloric content greatly in excess of his heat production. As a rule this does not happen until convalescence has been well established. If a typhoid patient loses 8 to 10 grams of nitrogen a day this represents the destruction of the equivalent of more than 200 grams of muscle substance daily.

Von Leyden and Klemperer demonstrated in the case of C. B. that they could diminish the nitrogen loss by giving large amounts of protein in the food or by giving calories in the form of fat and carbohydrate.

They were never able to bring their typhoid patients into nitrogen balance although they gave as much as 3,000 calories on some days and Shaffer and Coleman, using diets especially rich in carbohydrate, were the first to bring typhoid patients into nitrogen balance by giving 68 to 85 calories per kilogram per day (3,500 to 5,200 calories). The chart of one of their patients Z-O is given in Fig. 11. It will be noticed that the nitrogen balance became strongly negative when the caloric intake was diminished

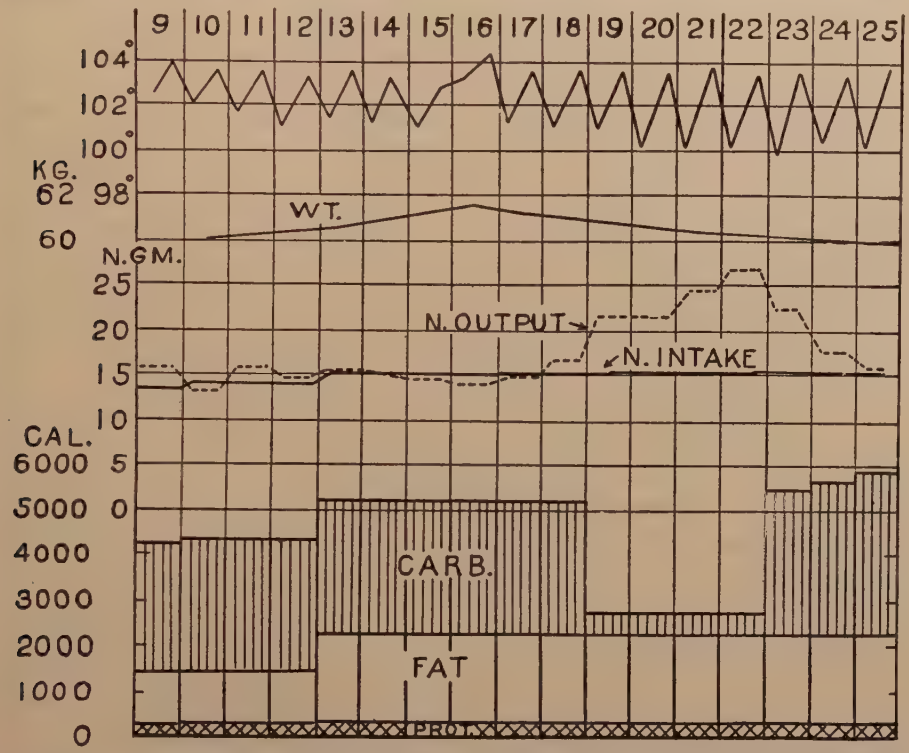

Fig. 11. Typhoid patient Z-O, studied by Shaffer and Coleman. He was maintained in nitrogen equilibrium by giving over 5000 calories per day. The line of dashes represents the urinary nitrogen plus 15 per cent of the food nitrogen, which is a liberal estimate for the amount excreted in the feces.

by reducing the carbohydrates and that equilibrium was not regained until the third day of the renewed 5,000 calory diet.

Grafe and others had taken the stand that the experiments of Shaffer and Coleman proved that there was no toxic destruction of protein in fever since nitrogen equilibrium could be attained. Grafe pointed out that protein furnished about the same percentage of calories in fever as in health. Shaffer and Coleman in New York and later Kocher, working in the clinic of Friederich v. Müller, were able to prove that fever patients could not be reduced to the nitrogen minimum of healthy persons even though they were given an amount of food which would more than cover

their caloric requirements. Kocher gave two normal men diets containing 5,089 calories and only 1.01 gm. nitrogen. On this diet the urinary nitrogen fell to about 3 grams and rose in one case to 3.77 gm. in the other to 4.69 gm. after a walk of 60 kilometers. On the day of the walks the protein must have furnished only about 2 per cent of the total calories. The bed-ridden fever patients on similar diets never excreted less than

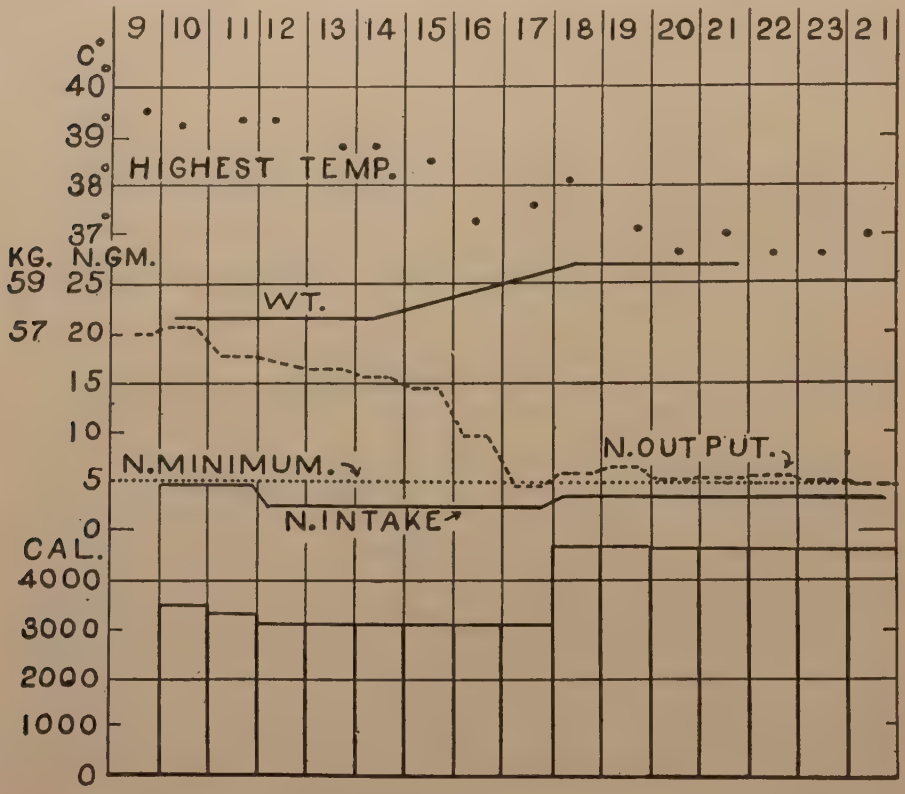

Fig. 12. Nitrogen minimum experiment of R. A. Kocher on patient with paratyphoid fever. The subject was given a liberal diet with low nitrogen content but the nitrogen elimination did not approach the normal minimum until the temperature had fallen.

10 grams of nitrogen in the urine until the temperature had fallen to normal. The results on one of his patients with paratyphoid fever are shown in Fig. 12.

This experiment shows the importance of studying the nitrogen minimum, the "wear and tear quota" of Rubner, which has been found to lie between 2 and 4 grams for healthy men. When a subject is on a diet which contains more than this amount of nitrogen the percentage of calories furnished by protein is merely a matter of proportion between caloric expenditure and consumption of protein either of the food or the

subject's own body. We have seen that Kocher reduced the protein to 2 per cent. After a meal containing a large amount of meat a normal man may derive more than 45 per cent of his calories from protein. Any percentage between these two points may be normal. The factor of muscular work which causes a great rise in total heat production scarcely raises the protein metabolism. Therefore the comparatively slight increase of heat production due to fever cannot account for the high nitrogen losses.

A normal man can be brought into nitrogen equilibrium if given sufficient food to cover the caloric requirement. This is accomplished without delay if the nitrogen intake is not greatly reduced but maintained at about 15 grams a day, which is the amount usually consumed by most individuals in health. If the nitrogen intake is suddenly reduced to the minimum of 3 to 5 grams it may take four or five days before the equilibrium is established at the low level. As we have seen above, this cannot be accomplished in typhoid fever. Coleman and Du Bois have arranged in a table (Table 4) their five patients who showed negative nitrogen balances when they were receiving 11 to 16 grams of nitrogen daily and calories more than enough to cover the daily expenditure which was actually determined in each case by measurements in the calorimeter. In a previous paper these same investigators had compiled a table showing the amount of food required to bring typhoid patients into nitrogen equilibrium. (Table 5.) From this it is clear that it requires about 58 to 85 calories per kilogram in the food to bring the patients into nitrogen balance although they produce on an average about 40 calories per kilogram, allowing for the moderate amount of muscular work performed by typhoid patients.

Table 4.—Chart Showing Negative Nitrogen Balances in Typhoid Patients Who Receive Food Calories in Excess of Calculated Heat Production

Patient	Dates or Days of Disease Inclusive	Days in Period	Range of Maximum Temperature, Degrees F.	Calculated Heat Production, Cal.[1]	Food Calories[1]	Food N, Gm.[1]	Nitrogen Balance Gm.[1]
Morris S..	Oct. 23-Nov. 3	12	102.8-104.6	2,266	2,863	16.4	—4.4
	Dec. 19-24	6	101.9-105.1	2,085	2,989	13.2	—2.4
Charles F.	Nov. 28-30	3	101.2-103.4	1,752	2,458	12.0	—4.6
Karl S...	Jan. 12-18	7	101.0-105.0	2,197	2,985	16.1	—3.2
	Jan. 19-22	4	98.8- 99.0	1,678	2,819	14.6	—1.9
John K...	Jan. 15-20	6	103.2-104.0	2,568			
	Days of Disease						
Frank W.[2]	11-14	4	104.0-105.4	2,200	2,250	11.3	—5.0
	15-19	5	103.0-104.0	2,238	3,320	15.3	—3.3
	20-23	4	101.0-103.6	2,054	2,362	15.9	—1.5

[1] Figures given are averages for twenty-four hours.
[2] Taken from Coleman and Du Bois, 1914.

TABLE 5.—FOOD REQUIRED TO BRING TYPHOID PATIENTS INTO NITROGEN EQUILIBRIUM

Name	Day of Disease	Range of Max. Temp.	Average Food Cal. Per Kg. Per 24 Hours	Average Food N. Per 24 Hours	Average N. Balance Per 24 Hrs.
R. N.[1]	20-24	104.4-102.0	71	10.9	+1.5
U. H.[1]	27-30	100.4-101.0	68	8.9	+0.4
Z. O.[1]	9-12	104.0-103.2	72	13.9	—0.2
Z. O.[1]	13-18	103.6-102.8	85	15.0	+0.6
Charles N.[2]	28-31	102.0-101-8	69	18.7	+6.0
Michael K.[2]	15-17	102.0-100.5	79	17.9	+1.5
Philip R.[2]	14-15	102.0-102.0	67	17.6	+2.7
John N.[3]	26-30	102.0-104.0	58	17.8	+1.9
Frank W.[3]	24-28	101.0- 99.6	74	20.3	+4.9
F. Ma.[4]	6- 8	103.1-103.6	45.5	10.5	—0.5
J. Gerl[5]	9-10	103.6-103.8	59.5	7.5	+0.4
J. Gerl[5]	16-21	100.9-103.4	76.6	8.1	+0.03

[1] Shaffer and Coleman.
[2] DuBois.
[3] Coleman and DuBois.
[4] Rolland.
[5] Rolland: Boy aged 10, weight 26 kg.

We may summarize the important features of the protein metabolism of typhoid fever as follows:

1. Patients on low diets show much greater protein losses than normal subjects on similar diets.
2. The protein minimum (wear and tear quota) is about three times as great as in health.
3. To bring patients into nitrogen equilibrium it is necessary to give 50 per cent to 100 per cent more calories in the food than the calculated caloric expenditure.

These have been considered ample proof that there is some factor in the infection which produces an abnormal breaking down of protein usually called a toxic destruction. This will be discussed more fully later.

The Effect of Food in Typhoid Fever.—We have seen in the previous paragraphs that the respiratory quotients show that during the fever ingested carbohydrates are quickly oxidized. During convalescence the large amounts of carbohydrate consumed replenish the glycogen stores, furnish material for the daily caloric needs and also supply an excess which may be converted into body-fat. We have seen that fats furnish the greater part of the calories during the febrile periods and that body protein is consumed in quantities much greater than in any group of normal men. We have also seen that nitrogen equilibrium can be attained only when patients are given unusually large amounts of food.

One of the striking phenomena of typhoid fever is the loss of appetite. Most patients desire only liquids since solid food is distasteful. This is partly due to the mental apathy, but experiments on animals

indicate that the toxins of the disease affect the cells of the stomach and also tend to diminish the hunger contractions. The appetite is doubtless affected also by the wretched condition of the mouth, which becomes apparent a few days after the onset of the fever unless great care be taken by the nurses to keep the mouth scrupulously clean. The coated tongue and sordes on the teeth are not an essential part of the disease, and when the nursing is adequate one may see a dozen typhoid patients in succession with tongues and teeth as clean as those of normal men. In such cases the appetite will return and the patients will consume large amounts of food if properly administered.

The older writers on typhoid fever speak of diarrhea with "pea soup stools" as characteristic of the disease, but in these days of liberal feeding

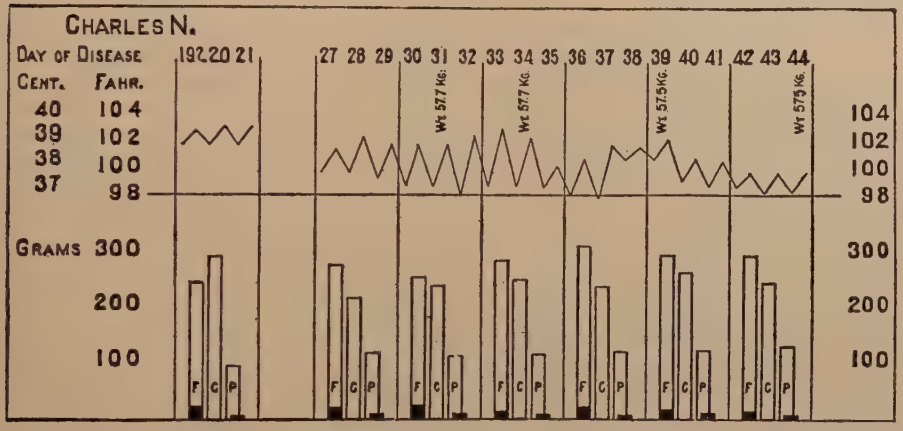

Fig. 13. Temperature chart of typhoid patient, Charles N., studied by Du Bois. The columns show the average daily weight of fat, carbohydrate and protein in the food; the solid bases represent the amounts unabsorbed. The feces were collected in three-day periods.

it is rare to find diarrhea, and the stools resulting from daily enemas are surprisingly normal. As long ago as 1882 von Hösslin found that typhoid patients absorbed food almost as well as normal men, although most of his patients had diarrhea. Several of his subjects during periods of practical starvation excreted in the feces 0.8 to 5.0 gm. of ether extract and 0.4 to 0.8 gm. nitrogen daily, this amount probably being derived from the intestinal tract itself. Several Russian investigators of Chudnowsky's clinic studied the absorption of food in typhoid fever. Aikinov, who included in the dietary 20 gm. blackberries, found from 4 to 6 gm. nitrogen in the stools and Grudziev, who gave a very liberal diet with 30 to 45 gm. nitrogen, found 4 to 11 gm. in the stools. These high figures are exceptional and are due either to irritating food or unusual amounts of protein in the ration. The influence of the high-calory diet of Shaffer and Coleman was studied by Du Bois and later by Coleman and Gephart.

Their results are shown in Table 6 and Figure 13.

TABLE 6.—ABSORPTION OF FOOD IN TYPHOID FEVER

Subjects	"Carbohydrate"		Fat		Nitrogen	
	Gm. Reducing Bodies in Stools	Per Cent of Intake	Gm. in Stools	Per Cent of Intake	Gm. in Stools	Per Cent of Intake
Normal Controls.....	Tr.	Tr.	3-6	5-8	0.5-1.0	5-8
Febrile Period, Typhoid	Tr.-3	Tr.-0.8	4-25	2-10	0.7-2.9	5-19
Typhoid Convalescence	....	....	6-8	2-5	1.5-2.0	10-12

Normal controls and typhoid patients on the Shaffer-Coleman high calory diet studied by DuBois and by Coleman and Gephart.

In general, we can say that von Hösslin has been confirmed in his statement that food is absorbed as well in fever as in health.

The work of Torrey on the intestinal flora in typhoid has been of great interest. When patients were given a high calory diet, rich in carbohydrates, he found that the flora became simplified in regard to the number of bacterial types and the fermentative organisms, particularly the Bacillus acidophilus, became dominant. If the flora originally showed a distinct putrefactive tendency the change was not great, but with a favorable initial flora the high carbohydrate diet finally resulted in stools that resembled those of normal infants in the dominance of the Bacillus acidophilus and even the presence of the Bacillus bifidus. This opens up a new field of speculation in regard to the effect of the fecal flora on metabolism. It is not at all improbable that many of the phenomena ascribed to changes in diet are really secondary to the establishment of a new type of flora in the intestine.

Specific Dynamic Action of Food in Typhoid Fever.—We have seen that during period of high temperature the caloric output is about the same in a group of liberally fed patients shortly after food as in a group of patients on low diets 14 or more hours after the last meal. In convalescence the patients studied shortly after food showed a distinctly higher metabolism, just as we find in the case of normal subjects. The specific dynamic action of food as described by Rubner manifests itself by an increased heat production during the time when the products of digestion are circulating in the blood and being consumed in the tissues. Coleman and Du Bois studied in the calorimeter the cause of the apparent absence of specific dynamic action in fever. Their results, as given in Table 7, show that the specific dynamic actions of protein and carbohydrate were much less than in the case of normal men or convalescents. It is not difficult to realize that the addition of a meal containing 8 to 9 grams of nitrogen would not increase the protein metabolism as much in the case

TABLE 7.—SPECIFIC DYNAMIC ACTION OF PROTEIN AND CARBOHYDRATE IN HEALTH, FEVER AND CONVALESCENCE

Subjects	Number of Experiments	Average Gm. of Nitrogen or Glucose in Food	Average Gm. Food per Kg. Body Weight Nitrogen or Glucose	Average Per Cent. Rise in Metabolism
Protein meal				
Two normal men	2	10.1	0.147	9.3
Four febrile patients	6	8.6	0.174	4.5
Four convalescents	5	10.2	0.217	16.6
Commercial glucose				
Three normal men	3	115.0	2.7	9.1
Two febrile patients	4	115.0	2.2	1.0
Three convalescents	3	115.0	1.6	9.8

of a typhoid patient who eliminates 20 to 24 gm. nitrogen daily as in the case of a convalescent or normal man excreting half this amount. When we look at Table 7 we see that the meal raised the percentage of calories obtained from protein only 5 per cent in the case of the febrile patients and 13 and 10 per cent in the case of normal controls and convalescents. The carbohydrate meal in almost all the cases decreased slightly the percentage of calories derived from protein and substituted carbohydrate. It seems probable that a combination of these factors serves to mask the specific dynamic action of carbohydrate. The question was admirably summed up by Lusk, in 1914. He called attention to the well known fact that if the metabolism be increased by lowering the environmental temperature there may be no specific dynamic action as usually induced by ingested food. In like manner if the metabolism be raised in fever, food ingestion may cause no increase. He also stated that since protein metabolism in fever can never be reduced to as low a level as is present in the normal organism, therefore protein ingestion in fever often merely serves to replace the protein already breaking up in increased quantity, and such protein ingestion would not then serve to increase the heat production.

The specific dynamic action of fat has not been sufficiently studied in typhoid fever. Coleman and Du Bois gave one patient 79 gm. olive oil and noted a rise of 3.4 per cent in the 2nd to 5th hours.

Body Weight.—There is nothing in the clinical aspect of typhoid fever more striking than the rapid loss of weight of patients who are taking small amounts of food. This subject is well reviewed by Coleman. (Fig. 14.)

The reasons for this melting away of body substance have been discussed in the previous chapters. The loss of weight is, for several reasons, greater than in the case of normal men who are fasting. The fever patient has a greater caloric output than any fasting man who does not take a

considerable amount of exercise. The fever patient does not show a progressive reduction in metabolism such as we find in starvation. The typhoid patient may have a negative nitrogen balance of 10 to 20 gm. a day, showing that he is losing much larger amounts of body protein than the professional faster. The latter loses relatively more fat, a tissue which contains a smaller proportion of water than body protein. The fever patient is losing more water through skin and lungs on account of the higher heat elimination and also during the periods of falling temperature there is a specific increase in the water vaporized from the skin.

Patients who are given the high calory diet in amounts which cover the energy requirement do not lose weight and sometimes gain during

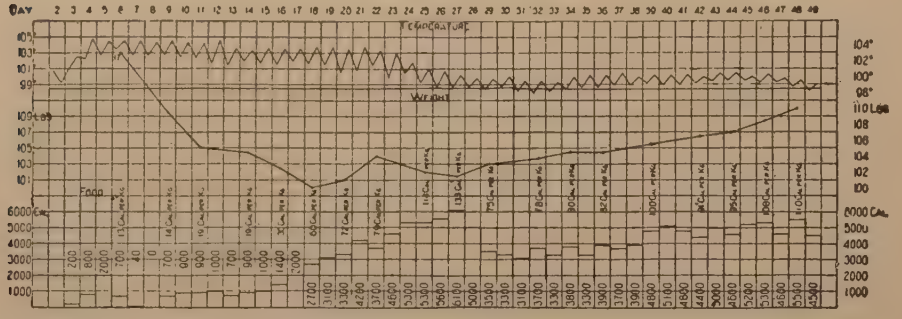

Fig. 14. Weight curve of typhoid patient who took but little food during the early part of his illness. After the 18th day of his disease the calories were increased rapidly and the patient began to gain weight. (Taken from Coleman, 1912.)

the fever, as is shown in Figs. 9, 11 and 12. It is possible that the gain in weight may be partly due to a retention of salt or an increased blood sugar which cause a retention of water, but it is difficult to see how a patient could help gaining weight if he were given more protein, fat and carbohydrate than he oxidized for a period of a week or more. There are no visible signs of significant changes in the water content of the body in any typhoid patients except those who are partly dehydrated on account of toxemia and insufficient fluids in the diet. The technic of establishing an accurate water balance in fever is so difficult that no one has yet made satisfactory determinations. The mere measurement of the fluids of the diet and the volume of the urine may give a water balance with an error of 50 to 100 per cent.

Urinary Constituents.—Complete analysis of the urine of typhoid fever patients will be found in the works of Ewing and Wolf, and Shaffer and Coleman. The creatinin excretion is increased during the period of fever, falling with or before the drop in temperature and establishing itself at a low level during convalescence. Shaffer found that normal subjects excreted 5.4 to 11.7 mg. creatinin per kilogram of body weight. In the febrile stages of typhoid Ewing and Wolf found one patient with an excre-

tion of 15.9 mg. per kg. (1.06 gm. per day). Shaffer and Coleman estimate the increase in their cases about 20 per cent above normal. In convalescence both groups of investigators obtained results as low as 4 to 5 mg. per kg.

Myers and Fine have recently found that a rise in temperature increases the rate at which creatinin is formed from the creatin of muscle tissue in autolysis and they believe that this accounts for the increased excretion of creatinin in fever.

Ewing and Wolf found that the creatin excretion of their patients during the febrile period was high, in one case reaching one gram of creatin nitrogen in twenty-four hours. Shaffer and Coleman also found large amounts in toxic patients and believed that it was due to the destruction of the patient's own muscles. When they were able to give their high calory diet they prevented the negative nitrogen balance and the creatin elimination disappeared.

In some fatal cases of typhoid Ewing and Wolf obtained high percentages of "rest" nitrogen. Coleman and Shaffer, who studied no fatal cases, failed to find an increased excretion. The latter authors found a moderate increase in the ammonia and uric acid at the height of the fever but were unable to establish any relationship between the xanthin bases and the febrile temperature. They found sugar in the urine in a very small proportion of the cases considering the large amounts of carbohydrate administered in the diets. Their patients showed a surprisingly constant sulphur to nitrogen ratio in fever and convalescence excreting between 7 and 8 parts of the former to each 100 parts of total nitrogen.

ADDENDUM TO METABOLISM IN TYPHOID FEVER

Van't Hoff's Law and the Basal Metabolism in Fever

In a recent article on the basal metabolism in fever (1921) the author had occasion to compare in graphic form the results obtained in six different fevers (Fig. 15). All were studied in the respiration calorimeter of the Russell Sage Institute of Pathology under identical experimental conditions, and all were plotted in the manner employed by McCann and Barr in tuberculosis. The ordinates represented the rectal temperature in degrees centigrade, the abscissæ the level of the metabolism, 100 being the average normal, 150 representing 50 per cent above the normal, etc. Each dot indicated a period of from one to three hours at the given rectal temperature. The diagonal lines were drawn to show the average direction of the swarms of dots. It became apparent that there was a striking similarity between the various fevers, although they were due to widely different causes.

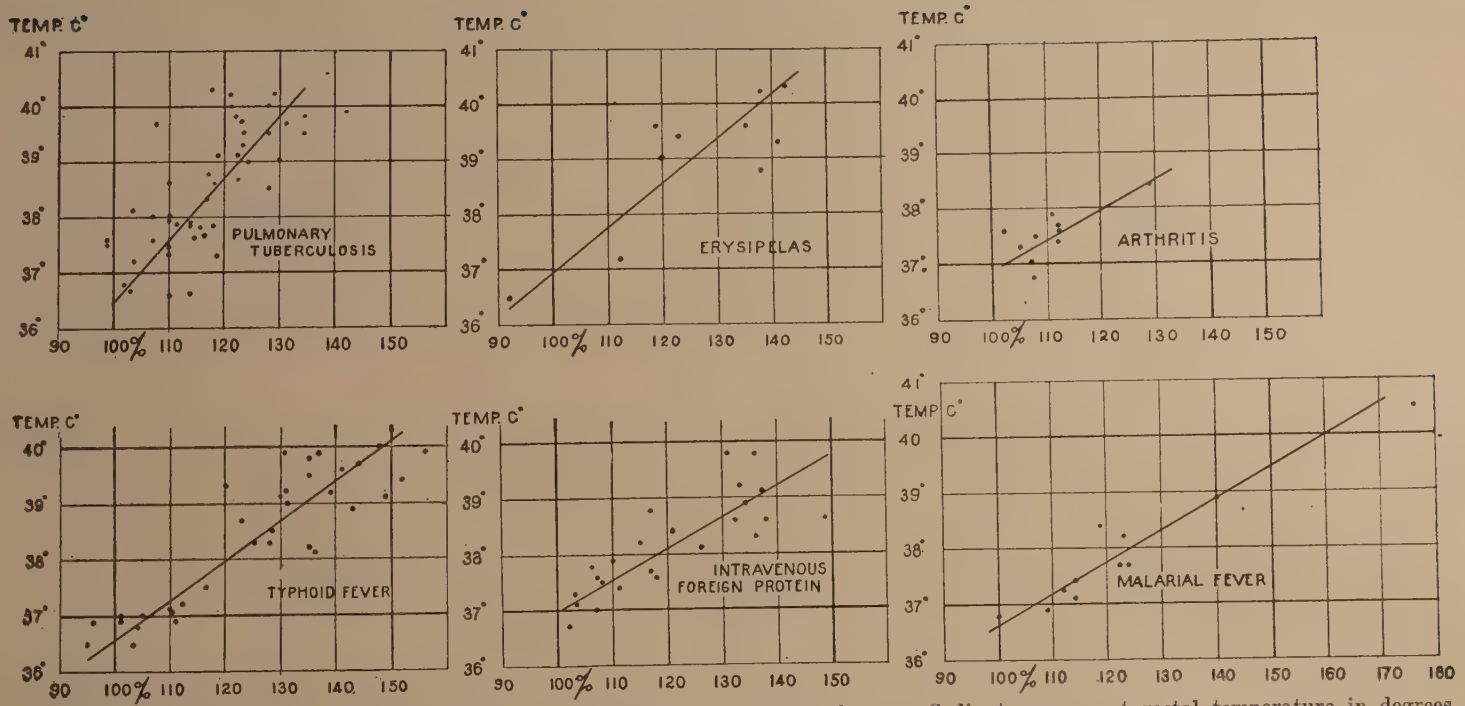

Fig. 15. Relationship of basal metabolism to temperature in various fevers. Ordinates represent rectal temperature in degrees centigrade, abscissæ the metabolism expressed in percentages of the average normal, e.g., 150 equals 50 per cent above the average. Each dot represents a calorimeter experiment of from one to three hours at the given temperature.

The results in all six conditions were next plotted on one chart (Fig. 16) and the average found by calculation. Lines were then drawn to show the range of 10 per cent above and below this average, and it was found that 82 per cent of the 137 determinations fell between these lines. Most of the cases in which the metabolism was more than 10 per cent below the average were tuberculosis patients with chronic undernutrition and an unusually low nitrogen metabolism. Most of the cases with basal figures more than 10 per cent above the average were typhoid patients with high nitrogen metabolism. On the whole, there was almost as much uniformity among the fevers as in a group of normal controls if due allowance were made for the increased metabolism in fever.

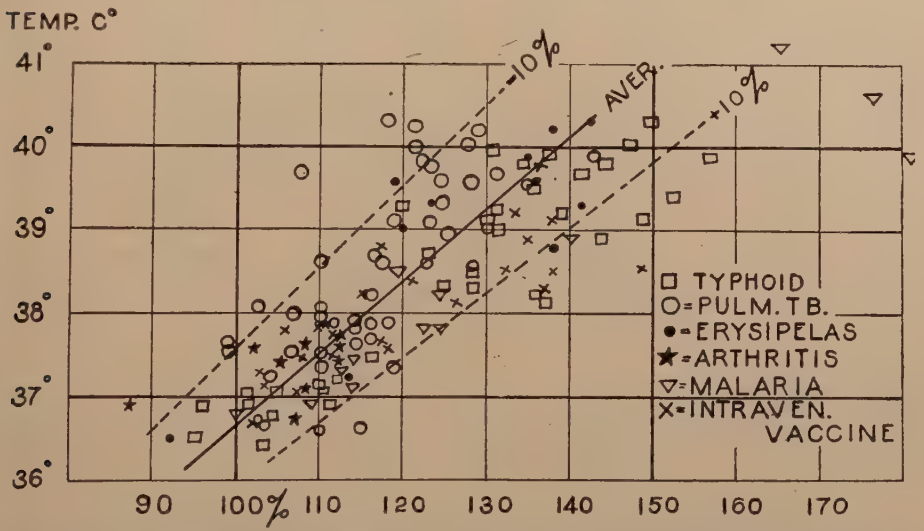

Fig. 16. Results in six different fevers grouped in one chart. The continued line shows the average and the dotted lines are drawn to represent metabolism 10 per cent above and 10 per cent below the average.

The average rise in heat production is about 13 per cent for each degree centigrade (7.2 per cent for each degree Fahrenheit). This enables us to calculate approximately the metabolism of a fever patient by finding his normal basal and adding the average increase for his degree of fever. In the case of toxic patients with great destruction of body protein there should be an additional ten per cent added and a similar addition in all other cases taking much food. If there is a high nitrogen elimination it is doubtful if food causes much specific dynamic action. Of course a further allowance of 10-30 per cent may be necessary if the patient is restless.

It is evident that the total oxidative processes in the body are increased by the rise in temperature of the body cells. This at once reminds us of the law regarding chemical reactions first enunciated by Van't Hoff,

the celebrated Dutch physical chemist. For ordinary temperatures this law can be expressed as follows: "With a rise in temperature of ten degrees centigrade the velocity of chemical reactions increases between two and three times." In other words, the temperature coefficient is usually between two and three. This means an increase of 30-60 per cent for the three degrees rise from 37 to 40° C. Practically all of the fever experiments are within these limits, and the average line shows a temperature coefficient of 2.3.

If we plot in the style used above all the various chemical reactions

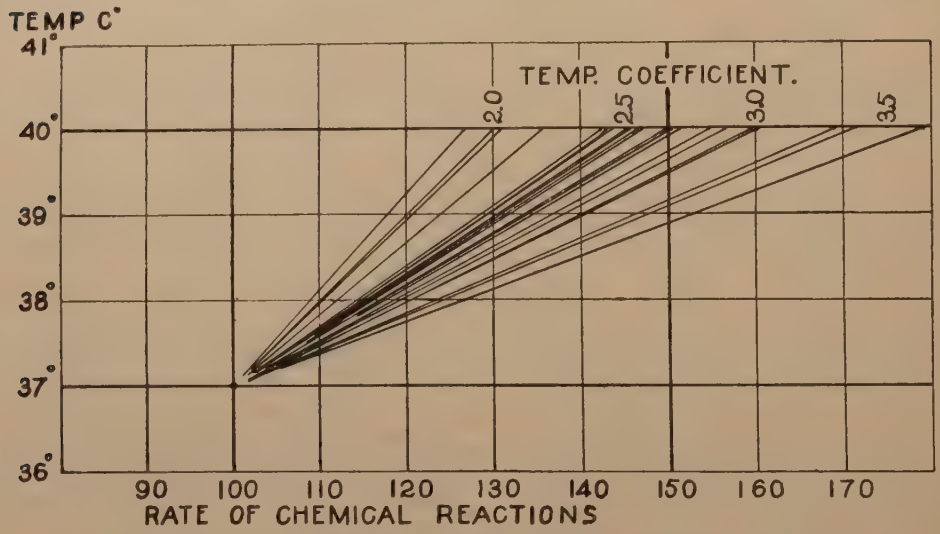

Fig. 17. The lines in this chart represent a number of typical chemical reactions taken from Van't Hoff and Kanitz. The slant of the lines shows the increase in the rate of the reactions as the temperature is raised. Note that the lines correspond closely to those which represent the total oxidations in the human body.

given by Van't Hoff and Kanitz (Fig. 17) we note that the lines have approximately the same slope found in fever. The patient responds to a rise in temperature in a manner which closely resembles the chemical reactions in a water bath. There is, of course, a tremendous difference between the simple medium of the test tube solution and the complex medium of the body fluids, but Kanitz has shown in his monograph that a large number of biological processes follow Van't Hoff's law.

Metabolism in Lobar Pneumonia

Lobar pneumonia differs from other fevers because there is a local lesion with a considerable amount of exudate which is rapidly formed and resolved. It is difficult to tell what proportion of the marked changes

in metabolism found in this disease should be ascribed to the exudate. We must certainly be careful in transferring results obtained in pneumonia to other fevers. No other infectious disease shows such a diminution in chlorid excretion or such a marked epicritical rise in nitrogen output.

Basal Metabolism.—We do not possess as much data regarding the respiratory metabolism in pneumonia as in other diseases. Investigators

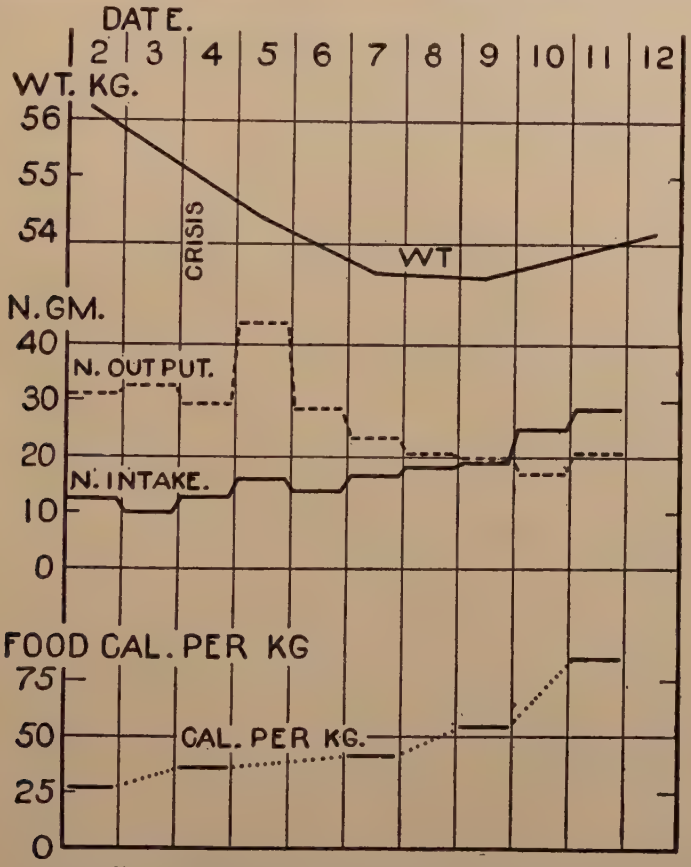

Fig. 18. Metabolism experiment by Svenson on patient with lobar pneumonia. The line of dashes shows the nitrogen excretion including the nitrogen of the feces which averaged 3 grams a day. Note that the urinary nitrogen rose to 40.8 gm. the day after the crisis. At the same time there was a rapid fall in body weight although the patient was receiving in his food almost enough calories to cover his requirement.

find these patients poor subjects on account of the dyspnea and coughing which interfere with any mouth-breathing or mask experiments. In respiration chambers it is almost impossible to keep the patients quiet for the long experimental periods. There are no published results giving the figures for delirious patients whose heat production must be two or three times as high as that of patients resting quietly in bed.

The respiratory metabolism was studied by Kraus, and later by Riethus who, grouping his figures with those of Kraus, estimated in one group of seven pneumonia patients, an average increase of 20 per cent above the normal and in another group of six, an increase of 55 per cent. Svenson, using technic which seems to have been excellent, found two patients with basal metabolism 50 and 70 per cent higher during pneumonia than after recovery from the disease. Grafe obtained results which were somewhat lower, but his patients were studied late in the febrile attack. Rolly, on the second day of the disease, found a respiratory quotient of 0.707 and an oxygen consumption of 5.98 c.c. per kg. and Min., which he considered about 50 per cent above the average normal.

Svenson's respiratory quotients in the febrile period were 0.702 and 0.700; in convalescence they rose to a level over 0.90 about ten days after the crisis.

In general, we can state that the respiratory metabolism in lobar pneumonia resembles that of severe typhoid fever with the same phenomena in convalescence. The heat production during the acute stages may be slightly greater but the period of increase is not so long.

Nitrogen Excretion.—For many decades attention has been directed towards the epicritical rise in nitrogen elimination which may occur a few days after the crisis. This is usually ascribed to the resolution of the pneumonic exudate with its rich protein content. In considering this subject we must remember that there is a curious retention of chlorids in the body during the fever with increased elimination after the crisis. The possibility of such a retention of nitrogenous metabolites must be considered also. A striking example of the epicritical rise in nitrogen is shown in Fig. 18, taken from the work of Svenson.

Loening did not find the epicritical rise as great as most of the earlier investigators. He believed that it could be accounted for by the resorption of the exudate on the strength of the following analyses obtained in the lungs of a patient dying of lobar pneumonia.

	Weight gm.	Total gm. N.	% N.
Normal left lung	588.	11.3	1.84
Consolidated right lung	1927.	41.4	2.15

Kocher, using his diet containing 3,400 to 4,200 calories and 2 to 4 grams of nitrogen studied two cases to ascertain the nitrogen minimum. During the fever the first patient excreted on an average 7 gm., the second patient 19.5 gm. of nitrogen a day. The second patient showed no drop in nitrogen excretion until the third day of normal temperature, when it reached 13.6 gm. and then fell by the 5th day to 11.3. Many

other fevers show a similar high excretion of nitrogen for several days after a fall in temperature.

Lanz gives a series of six cases in which he determined the daily loss of nitrogen in the sputum. The figures are about the same as in tuberculosis, ranging from 0.3 to 1.7 gm. per day. In bronchitis the nitrogen loss was about half this, in gangrene of the lung it reached as high as 2.5 gm. on one day.

Chlorid Metabolism.—The excretion of chlorids is diminished in almost all fevers, malaria being a notable exception, but the diminution is most striking in pneumonia. There may even be a complete disappearance of chlorids from the urine for several days. The chloride-poor fever diet, consisting chiefly of milk, would naturally cause some diminution, but the chlorids remain low even if they are given in large amounts in the food. The pneumonic exudate, according to Hutchinson, will account for only one-third or one-half of the total amount retained.

Terray(*a*), one of the earlier investigators of the subject, studied the chlorids in five pneumonia patients and found retention which increased up to the crisis and then less retention for a few days. After the eleventh day there was a negative chlorid balance. Terray believed the retention of sodium chlorid was associated with water retention.

Peabody(*b*) has made some analyses of the chlorin in the solidified lungs as compared with the normal lungs.

	Solidified Lung	Normal Lung
	Gm. Cl.	Gm. Cl.
Case 1	2.838	1.022
Case 2	2.916	0.715

Practically all of the observers who have made blood analyses have found low chlorids in the blood serum. This conflicted with the theory that the kidney was responsible for the retention. All doubts have been removed by Snapper(*a*) and more recently by McLean(*b*). The former found in five pneumonia patients figures for NaCl in the serum between 5.40 and 5.60 gm. per liter, all below his normal "threshold" value of 5.60, which corresponds closely with Ambard's figure of 5.62. He points out that under such conditions one would not expect the normal kidney to excrete chlorids. In the one case where the serum chlorids were above the "threshold" the salt was excreted according to the formula that Snapper found in normal cases. McLean made sixty analyses in thirteen cases of pneumonia and found that the plasma NaCl was almost below 5.62 gm. per liter, the normal threshold. He found that in fever the threshold was even depressed to about 5.42. At the time when the concentration of salt in the serum increased the excretion through the kidney was re-

sumed. The results obtained by McLean in one of his cases are reproduced in Fig. 19.

Where is the chlorin retained? Numerous attempts to discover large increases in the salt content of various parts of the body have failed. The

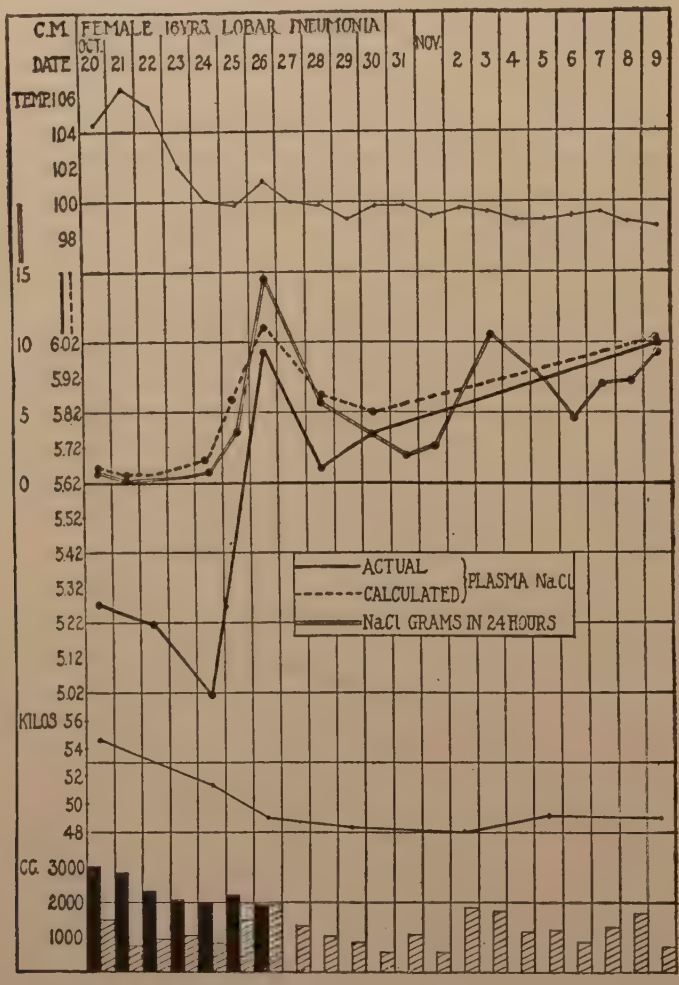

Fig. 19. Patient with lobar pneumonia studied by McLean. Before the crisis the chlorid excretion was almost nil and the plasma chlorids far below the normal level. After the crisis the chlorids in the blood rose sharply and the excretion of salt jumped to 15 grams. At the same time there was an increase in the volume of urine and a loss of weight. The solid blocks at the bottom of the chart show the fluid intake, the blocks with diagonals, the output. The dotted line of "calculated plasma chlorid" was derived from a formula by McLean.

older analyses are well reviewed by Hutchinson and by Garrat. Peabody has recently disposed of the hypothesis that much salt could be retained by the skin, finding normal figures in the skin of pneumonia patients who

had shown salt retention and died. Every one seems to be agreed that the chlorin and sodium are generally distributed throughout the tissues. Snapper has found that when sodium sulphate is added to normal blood the chlorin passes from the blood cells into the fluid and that in pneumonic blood it passes in the opposite direction. He believes that the chlorid retention is caused by a modified permeability of the tissue cells. Medigreceanu and others have found that rabbits with pneumococcal septicemia do not show chlorid retention, so there does not seem to be anything in the toxin itself which causes this condition.

Sandelowsky has found that patients who retained their weight during the febrile period and lost weight suddenly after defervescence showed a diminished concentration of proteins in the blood with a return to normal after the loss of weight. This indicated an hydremia in pneumonia which would account for a considerable retention of chlorids in order to maintain the osmotic pressure of the blood. Rowe confirmed the decrease in total protein, obtaining an average of 6.2 in pneumonia as opposed to his average of 7.94 for normal controls. The globulin percentage, on the other hand, was increased to 40, which was almost double the normal.

Roehrich and Wiki have found an extraordinary rise in the sodium chlorid excretion in the fourth week of convalescence.

Blood Constituents.—With the high protein metabolism of lobar pneumonia it is not surprising to find some increase in the nitrogenous constituents of the blood. A few of the cases reported, however, seem to have an actual retention by the kidneys. Tileston and Comfort, who give as their normal figures for non-protein nitrogen 22.9 to 25 mg. per 100 c.c., found that out of fourteen cases of pneumonia six showed a moderate degree of retention, that is, more than 35 mg. non-protein nitrogen in the blood, the highest figure being 50 mg. The retention reached its maximum toward the crisis and disappeared early in convalescence. It was not dependent on the absorption of exudate, for it occurred before resolution took place. Most of their patients showed albumin and casts in the urine, two showed impaired renal function as estimated by the phenolsulphonephthalein test, five gave normal results.

Schwartz and McGill analyzed the blood urea in twenty cases of pneumonia and found an average of 40.5 mg. per 100 c.c., with a range between 12 and 104. Only one patient with blood urea over 60 recovered. They record that seventeen out of their twenty patients had toxic nephritis. Their normal controls showed a range of 10 to 25 mg., with an average of 12.9. Whipple and Van Slyke(*c*) found in lobar pneumonia the non-protein nitrogen of the blood between 42 and 85 mg. per 100 c.c.

Frothingham(*b*), in four cases of Type 1 pneumonia, found the phthalein test normal and blood urea slightly increased in two cases. In six cases of Type 4 pneumonia two had phthalein tests just below normal and two had slight increase in blood urea. He concludes that during febrile attacks

the new kidney functions tests do not show kidney damage much better than the older methods of urine examination.

Blood sugars seem to be increased as in other fevers. Rolly and Oppermann found between 0.106 and 0.122 gm. per 100 c.c. Hollinger, in most of his cases, found between 0.114 and 0.145 gm. One patient went as high as 0.168, sinking to 0.096 fourteen days after the crisis. John has recently reported a series of analyses ranging between 0.07 and 0.18. He obtained excellent results clinically by the intravenous administration of 250 c.c. of 10 per cent glucose solution. Immediately after this injection the blood sugar was about double its former concentration though it seldom rose above 0.3.

Acidosis in Pneumonia.—The estimation of the degree of acidosis in pneumonia presents unusual difficulties. The abnormal relationships in oxygen and carbon dioxid content of venous and arterial blood, the dyspnea, the chlorid retention may upset our calculations entirely. The carbon dioxid content of the blood in fever was studied by Kraus and more recently by Peabody(*a*), using modern methods. The latter made ninety-one analyses in twenty-six cases and found the CO_2 content between 40 and 50 volume per cent in the acute stages. He concludes that a diminution of the CO_2 was found in all but a few cases of pneumonia and that it was not necessarily in proportion to the severity of the disease, though the lowest figures were usually found in the severe cases and terminal stages. As a rule it was proportional to the output of ammonia, but bore no relation to the chlorid excretion or temperature curve. The CO_2 might be low for some days after the patient was afebrile. Acetone was found in only two cases. Pick has found a significant decrease in the acidity of the urine and even the appearance of alkalinity occurring 36 to 48 hours after the crisis. This he believes due to a considerable increase in the excretion of sodium caused by the absorption of the exudate. Palmer and Henderson found that during pneumonia large amounts of sodium bicarbonate were required to make the urine alkaline and Palmer(*c*) ascertained that an inorganic acid of unknown nature was being excreted in the urine and that analysis of the plasma CO_2 combining capacity indicated that the acidosis was seldom severe. Frothingham(*a*) has confirmed the work of earlier investigators in finding in some cases high ammonia excretion with an increase in the amount of sodium bicarbonate required to alkalinize the urine. One of his fifteen cases showed acetone in the urine. In some the CO_2 content of the alveolar air indicated acidosis, in others the reverse.

Miscellaneous Metabolites.—Much of the work on the inorganic constituents of the blood and urine is fragmentary and inconclusive. The careful work of Peabody indicates that during the fever there is a retention of Cl, Na and Ca in the body, while there was a normal excretion of K and Mg. The Ca and Mg in the blood were apparently slightly lower than normal. The excretion of phosphates was irregular.

Wolf and Lambert have published elaborate analyses showing the partition of nitrogen and sulphur in nineteen cases of pneumonia. During the fever they found excessive amounts of creatinin, and in the severe cases large amounts of creatin also. They conclude that the sulphur excretion runs more or less parallel with that of the nitrogen but shows considerable variation in some cases.

Jobling, Petersen and Eggstein(*c*), in studies on the serum ferments and antiferments, have found that the crisis in pneumonia is usually accompanied by a decrease in serum antiferment, a mobilization of non-specific protease in the serum, an increase in serum lipase and decrease in the proteoses and non-coagulable nitrogen of the blood. They believe that the crisis is attended by the beginning of an active autolysis which is dependent on an altered ferment-antiferment balance. They consider that the fibrin and leucocytic débris are potential sources of toxic substances.

TABLE 8.—BLOOD CHEMISTRY FINDING IN INFLUENZAL PNEUMONIA (WELLS)

Clinical Type of Disease	No. of Cases	Chlorids Av. Per Cent	Creatinin Av. Mg. Per 100 c.c. of Blood	Urea N. Av. Mg. Per 100 c.c.	Uric Acid Av. Mg. Per 100 c.c. of Blood
Mild	8	0.62	1.06	16.9	3.75
Mod. severe	24	0.60	1.58	21.9	3.75
Very severe or fatal	26	0.56	1.49	25.2	4.98
Day of disease					
First	4	0.51	1.94	16.0	4.59
Second	16	0.64	1.62	19.8	4.53
Third	9	0.52	1.54	21.2	6.06
Fourth	5	0.58	1.22	23.5	3.02
Fifth	9	0.56	1.06	22.1	3.11

Our knowledge of the changes in metabolism in influenzal pneumonia is not yet extensive. Wells, in a recent article, has published a large series of blood analyses showing that the epidemic disease with its complicating pnumonia resembled in its metabolic aspects other fevers of similar duration and severity. (Table 8.)

Metabolism in Tuberculosis

Tuberculosis in its milder forms escapes diagnosis so often that we can be certain that many unsuspected cases have been included among the so-called normal controls. It is doubtful if the metabolism departs from the normal in the incipient stages of the disease. On the other hand, the severe, fulminant types may resemble closely typhoid fever or lobar pneumonia with the profound metabolic disturbances which characterize these infections. Between these two extremes come the large mass of tuberculous patients with involvement of various organs and toxemias

of every grade of severity, perhaps complicated by mixed infections. Obviously it is impossible to make generalizations and say that the metabolism in tuberculosis is thus and so.

The chemical pathology of tuberculosis was thoroughly reviewed by Ott and his collaborators in 1903, and the chapter on metabolism particularly well treated by May.

Total Metabolism.—Löwy found a considerable increase in the oxygen consumption of a patient with miliary tuberculosis of the lungs but some of his respiratory quotients are so much lower than those found by more recent investigators that there seems to have been some technical difficulty with the methods employed. Grafe, using a respiration chamber, studied 12 patients with pulmonary tuberculosis and found the metabolism increased from 0 to 50 per cent, with an average of 25 per cent above the normal. In 5 patients with other types of tuberculosis the increases were between 15 and 25 per cent. Rolly, in a patient with latent tuberculosis, found an oxygen consumption of 3.9 to 4.9 c.c. O_2 per kilogram and minute, 3.9 being about the average for normal controls. Barbour(*c*)

TABLE 9.—METABOLISM IN TUBERCULOSIS AS GIVEN BY MCCANN AND BARR

Name	Age	Wt. Kg.	Calories Per 24 Hrs.	Per Cent Rise Above Av. Normal	Type of Tuberculosis
Chas. G.....	31	52.4	1668	13	Active tb. of pleura and peritoneum.
Trellis H.....	24	51.6	2026	35	Temp. 40° C. coughing. Active tb. lungs and lymph nodes.
Robert W....	39	53.4	1886	29	Temp. 40.1-39.4. Pleurisy with effusion.
Geo. P.....	18	58.5	1812	11	Acute miliary tb. with cavity at right apex.
Spencer C....	46	44.4	1534	12	Active pulm. tb. with cavity.
Edith B.....	20	44.6	....	2	" " " " " Afebrile.
"	"	...	1598	15	Febrile, restless.
Harry G.....	18	42.7	1746	21	Active pulm. tb. Bilat., infiltration with cavity.
Joseph D.....	33	59.0	1558	—3	Inactive. Infiltration both upper lobes and left base.
Anna H.....	17	41.0	1728	28	Bronchopneumonic phthisis.
Michael C....	33	50.0	1956	27	Cavity in lung. Involvement of larynx.
John H.....	25	45.0	1678	15	Active bilateral infiltration.
Wm. H.....	31	49.7	....	9	Active pulm. tb. Inactive tb. of hip. Temp. 38. quiet.
"	"	...	1658	21	Temp. 38.6 coughing.
John S.....	28	62.3	2030	14	Active pulm. tb. Mitral stenosis and regurgitation, compensated.
Geo. M.....	31	49.1	1852	28	Active pulm. tb. with cavity.
Joseph R.....	36	61.3	1697	3	Pulm. tb. with cavity. Chronic nephritis with edema and hypertension.

studied three tuberculous patients while investigating the action of antipyretics and found the heat production only 3 to 4 per cent above the average normal. McCann and Barr have recently made careful studies, using the Sage respiration calorimeter. Their findings are shown in Table 9.

It will be seen that the total calories per day for the basal metabolism ranged between 1,530 and 2,030, and that the lowest was 3 per cent

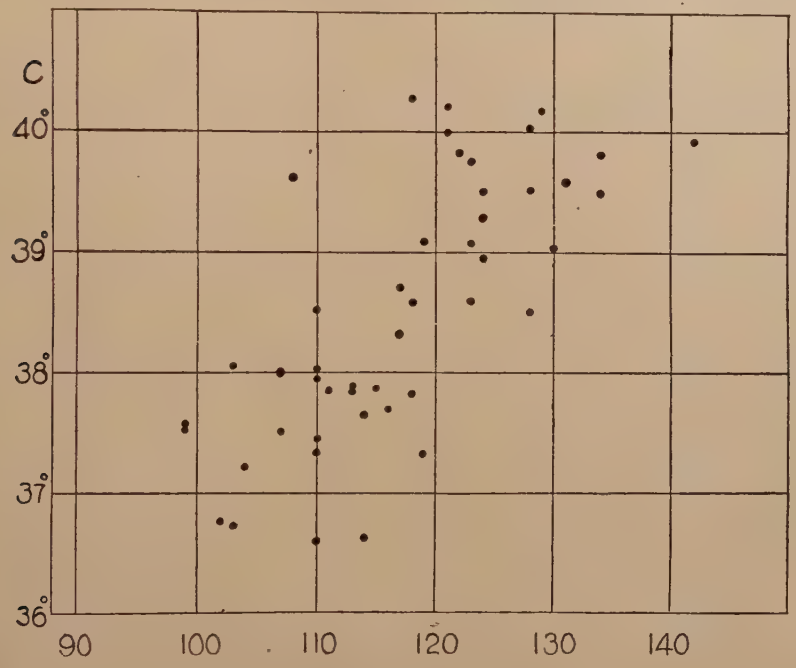

Fig. 20. Results obtained by McCann and Barr in tuberculosis, showing relationship of basal metabolism to temperature. The abscissæ show level of metabolism in terms of the average normal, 100. Most of the observations made when the temperature was above 39°C. were 20-30 per cent above the normal basal average.

below the average normal and the highest 35 per cent above. These authors bring out the interesting point that the patients, after several weeks or months of illness, were producing almost exactly the same amount of heat as they did at the time of their best weight before the onset of symptoms. The increase caused by the infection compensated for the decrease due to loss of weight and undernutrition. Fig. 20, taken from their work, shows that the metabolism tends to be proportional to the temperature. This may be due to the temperature itself or to the toxic agent which causes a rise in both.

The figures for the direct and indirect calorimetry differed by 5 per cent, the indirect method giving higher results. This difference, which is

considerably greater than was found in other fevers, may have been due to the fact that almost all of the observations were made with a rising temperature and under such conditions there is a tendency for the calculation by the direct method to be too low since the changes in the rectal temperature are not equal to the changes in the average body temperature.

Character of Foodstuffs Oxidized.—In all the modern work the respiratory quotients are the same as those found in normal people of similar state of nutrition. There are no indications of abnormal metabolism of fat or carbohydrate. There is, on the other hand, evidence of a toxic destruction of protein in many cases. This does not seem to be as great as in the more acute fevers. May,. in Ott's book on the chemical pathology of tuberculosis, devotes seventy pages to this subject, reproducing many tables of experimental data from various investigations. In discussing the afebrile cases he concludes that many tuberculous patients, or rather all of them at some time in the disease, show a pathological increase of protein metabolism in the sense of a toxic destruction. This he believes is dependent on the production and resorption of poisonous substances from the areas of tuberculous involvement. His tables of nitrogen balances in febrile cases show consistent losses, sometimes as great as 10 to 12 grams a day, but the data regarding the caloric intakes are incomplete. The injection of tuberculin seems to have no effect unless it raises the temperature, in which case there is an increased tendency towards a negative nitrogen balance.

Rolland has been able to bring five tuberculous patients with various types of the disease into nitrogen balance by administering 33 to 50 calories per kilogram per day in the food with 9 to 13 grams of nitrogen. It is not certain whether or not this ration covered the caloric output. Kocher gave three patients diets containing 2,900 to 3,800 calories and 1.1 to 2.3 gm. nitrogen and found that they excreted 12 to 18 gm. nitrogen in the urine, or about five times as much as normal men under similar circumstances. McCann and Barr repeated these experiments in the nitrogen minimum in tuberculosis, giving more calories than were required to cover the output as determined in the calorimeter. They were unable to reduce the excretion below 5 to 6 gm. The results in a case of acute miliary tuberculosis with a cavity at the apex of the right lung are shown in Fig. 21. The nitrogen minimum was much lower than in other fevers with the same level of temperature but not so low as normal.

Sputum.—Ott has given a careful review of the chemistry of the sputum in tuberculosis. Many investigators have studied this subject. Among them Lanz has found nitrogen losses ranging between 0.2 and 1.7 gm. a day with an average of 0.68 per cent. Such losses, when continued for months, are of considerable importance. This nitrogen does not represent recently metabolized protein as does the urinary nitrogen, but rather the loss of tissues built at some previous period.

The Effect of Food.—In many cases of tuberculosis there is a factor which causes diminution in the appetite, and this must be the chief cause of the loss in weight. We have seen that a patient's basal caloric requirement is about the same as when he was at his best weight in health. If we add to this enough of an excess to maintain nitrogen equilibrium we do not exceed the amount of food consumed by an active healthy man. The human appetite which will respond to the demands of healthy labor will not respond to the abnormal demands created by toxins.

Once eaten, the food is absorbed by the intestine about as well as in health as shown by the numerous authors quoted by Ott and May. In those cases, however, in which there is profuse diarrhea due to extensive involvement of the gut the losses of nitrogen and fat may be considerable. Friederich Müller(*b*) describes a case in which 33 per cent of the ingested fat was lost in the stools.

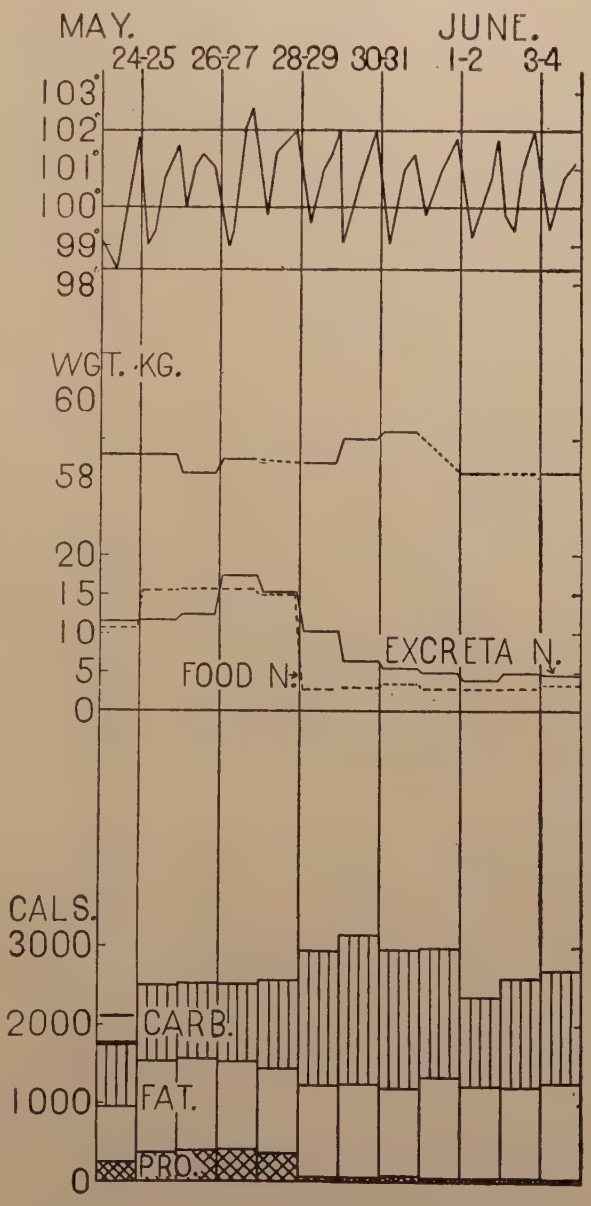

Fig. 21. Nitrogen minimum in tuberculosis as given by McCann and Barr. George P., with basal metabolism of 1812 calories, was given about 2500 calories which was more than enough to cover his requirement. The food nitrogen was diminished to about 3 gm. but the excretion only fell to 5 gm., a level slightly higher than in normal controls.

The specific dynamic action of food in tuberculosis has received little attention up to recent times. McCann and Barr have studied the effect of a meal consisting of 350 gm. chopped meat containing 70 gm. protein and 28 gm. fat. The results are shown graphically in Fig. 22. One tuberculous patient in three hours following this rather large meal of meat showed an average increase in heat production of 16 per cent, a second patient 18 per cent. Normal controls gave practically the same rise, averaging 21 per cent. Such an increase in the oxidative processes throws additional work on the heart and lungs. It may possibly act like mild

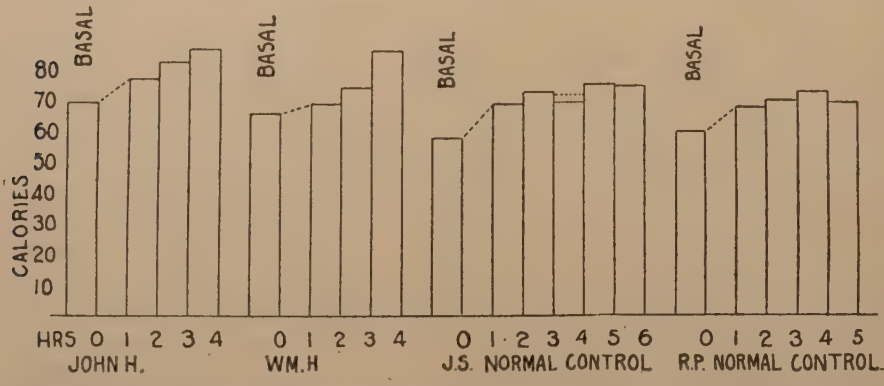

Fig. 22. The specific dynamic action of protein in tuberculosis patients as compared with normal controls. In each experiment the first column shows the basal metabolism, the subsequent columns show the heat production 1-6 hours after a meal of 350 grams of chopped beef. (Taken from McCann and Barr.)

exercise in raising the body temperature to a light extent. The extra heat would be helpful only in the case of a patient exposed to extremely cold weather. McCann and Barr issue the timely warning that clinicians must remember the specific dynamic action when giving large amounts of food.

We know very little about the specific dynamic action of fats and carbohydrates in chronic tuberculosis, but there is no reason to doubt that large meals of these substances cause a considerable rise in metabolism just as in health. We have seen that the specific action of protein and carbohydrate was found to be less than normal in typhoid fever, probably being masked by the great increase in protein metabolism found in this disease. Severe cases of tuberculosis may resemble typhoid fever in this respect.

Temperature Regulation in Tuberculosis.—Two striking clinical phenomena of tuberculosis are the rapid fluctuations in body temperature and the night sweats. von Schrötter, in Ott's book, reminds us that we must not confuse the night sweats of an early case in which the temperature fluctuations are slight with the profuse sweating of advanced cases in which there are sharp remissions in the temperature. With failing temperature we find sweating in almost all diseases, so this is easily explained

as the normal method of increasing heat elimination. Sweating without a fall in temperature is puzzling and we cannot be altogether satisfied with von Schrötter's suggestion that the toxins of the tubercle bacillus stimulate the "sweating center" in the medulla and cord earlier than the "heat centers." He has some support for the theory in the occurrence of one-sided sweats which affect only half the body.

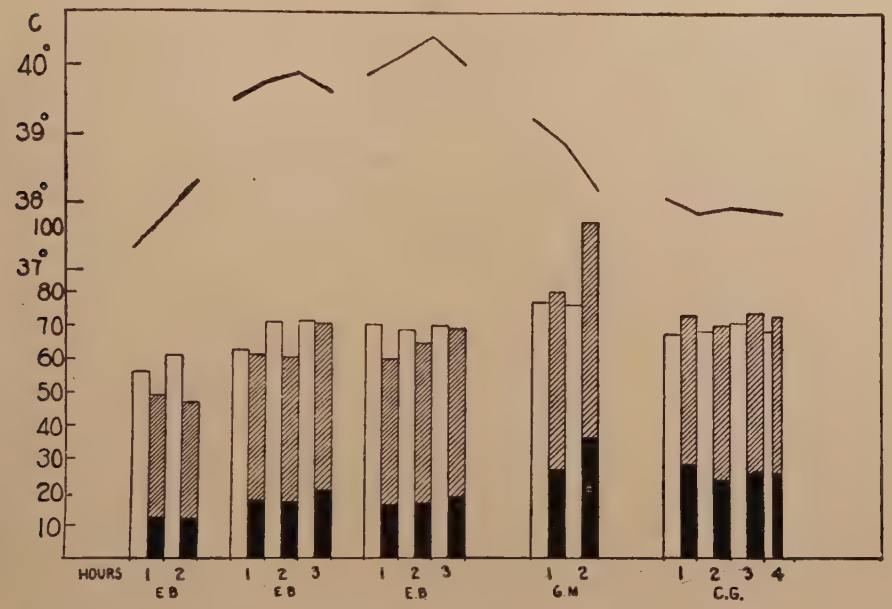

Fig. 23. The mechanism of the rise and fall of body temperature in tuberculosis as determined in a respiration calorimeter by McCann and Barr. Five different experiments are arranged according to the curve of the rectal temperature (upper line). The unshaded columns represent the heat produced as determined by the indirect method. The shaded columns show the heat lost from the body by vaporization (solid black) and by radiation and conduction (diagonal lines). Periods are for one hour for each pair of columns. Note that the production greatly exceeds the elimination during the rise of temperature. The fall of temperature is accomplished by an enormous increase in radiation, conduction and especially vaporization.

Staehelin(*a*) attacked the problem with a brilliant conception of its significance but encountered such technical difficulties that his results do not seem reliable. McCann and Barr tried in vain for several years to catch a patient with one of these typical night sweats in the calorimeter. They have, however, obtained much important data regarding heat production and heat elimination during the rise and fall of body temperature. Their results are shown graphically in Fig. 23.

With a rising temperature the heat production increases and exceeds the elimination. At the height of the fever the elimination catches up with the production. During the fall there is an enormous jump in radiation and conduction and especially in vaporization.

Data concerning the water elimination through skin and lungs have been published by Schwenkenbecker.

Blood Constituents.—The blood sugar is increased in tuberculosis as in other fevers. Hollinger reports 153 mg. glucose per 100 c.c. blood in a case of miliary tuberculosis. Rolly and Oppermann found in one febrile patient 114 mg. and in a patient with dyspnea but not fever 86 to 91 mg. They believe that the sugar is increased in infectious diseases but not in proportion to the temperature and that the hyperglycemia is caused in part by the fever and in part by the toxins.

Tileston and Comfort found a considerable retention of non-protein nitrogen in the blood in two out of three cases of tuberculosis studied. Schwartz and McGill found an increase in blood urea in two out of seven cases. One patient with acute miliary tuberculosis had 60 mgm. urea per 100 c.c. of blood.

Janney and Newell have recently studied in detail a series of diabetic patients showing pulmonary tuberculosis as a complication and have come to the conclusion that the tuberculous lesion does best with judicious undernutrition. The patient should be kept with his urine sugar-free, but fasting should be avoided as unnecessary and somewhat dangerous. In three cases of active tuberculosis they found the basal metabolism normal and considered that the tendency towards increase from the pulmonary lesion was offset by the lowered metabolism found in undernourished diabetics. Three patients with diabetes and inactive tuberculosis gave results 15 to 37 per cent below the average normal.

Erysipelas

In erysipelas there is frequently a severe grade of toxemia which resembles that of typhoid fever, and it is not surprising that in the two diseases there are striking similarities in the metabolism. The fact that one is a streptococcus disease with its local lesion in the skin and the other a bacillary infection with its local lesion in the intestine seems to make but little difference.

Total Metabolism.—Several determinations of the total caloric output have been made in facial erysipelas by Riethus and Grafe(*d*)(*h*) and in recent times by Coleman, Barr and Du Bois, using the Sage respiration calorimeter. Riethus found an increase of 41 per cent in the metabolism, Grafe in one case with a temperature of 39.5° found the heat production 40 per cent above the level which it reached after recovery. The results obtained by Coleman, Barr and Du Bois are shown in Table 10.

The respiratory quotients resemble those found in typhoid patients in a similar state of nutrition and there is the same evidence of toxic destruction of protein. Loening in a comparative study of the nitrogen losses in

TABLE 10.—RESPIRATORY METABOLISM IN ERYSIPELAS

Summary of the calorimeter experiments of Coleman, Barr and Du Bois

Patient	Date	Av. Rect. Temp.	Av. Pulse	Av. R. Q.	Rise Above av. Norm. Basal Metab.	Remarks
Arshel A.	Oct. 13, '16	39.4	98	0.74	23	Rising temp.
" "	" 15	39.6	85	0.75	19	Falling temp.
James W.	Oct. 17	36.5	59	0.84	—8	First day normal temp.
Odysseo B.	" 27	38.8	67	0.76	38	Rising temp.
Robert H.	Nov. 1	39.6	104	0.75	35	Period of high temp.
" "	" 3-4	40.3	104	0.77	42	Rising temp.
" "	" 4-5	39.3	105	0.74	41	
" "	" 8	37.2	83	0.78	12	First day of low temp.
Joseph S.	Mar. 6, '17	40.2	94	0.78	38	Period of high temp.
" "	" 9	39.0	82	0.78	20	" " " "

various fevers published the results in eight cases of erysipelas. A striking curve is shown in Fig. 24. Rolland in one case with a range of maximum temperature between 37.5° and 39° C. gave 46 calories per kilogram in the food with 12.1 gm. of protein daily and found a negative nitrogen balance averaging 0.67 gm. per day but considered this as evidence against a toxic destruction. Kocher was able to administer to four erysipelas patients diets containing 3,200-4,300 calories and only 1.8-2.2 gm. nitrogen. On such diets normal men, even though they performed severe muscular exercise, came to a minimum nitrogen excretion of 2-3 gm. per day. The erysipelas patients excreted 9-20 grams of nitrogen even after several days of this diet. Grafe, one of the chief opponents of the theory of toxic destruction, confirmed these results. He gave an erysipelas patient a diet containing 66 calories per kilo and practically no protein. The urinary nitrogen dropped from 25.9 gm. a day to 7.7 gm. on the fifth day, but would not fall below this point. Coleman, Barr and Du Bois found the same high nitrogen losses in patients who were receiving in the food more calories than the total expenditure as determined by the calorimeter. In all of these experiments there are numerous indications that the nitrogen losses are not dependent on the high temperatures since they continue for several days after the fever has disappeared. They seem to prove in every possible way that there is some toxic agent which causes a much higher metabolism of protein than in health. They show also that the administration of abundant food, rich in carbohydrates, diminishes the nitrogen losses.

Analyses of Blood and Urine.—Hollinger has found in erysipelas blood sugar contents ranging from 0.114 to 0.131, about the same degree of hyperglycemia as he found in other fevers.

The various urinary constituents have been determined by most of

the investigators who have studied the nitrogen metabolism. Unusually complete analyses were made by Kocher. He found during the febrile periods considerable increase in the excretion of creatinin at the height

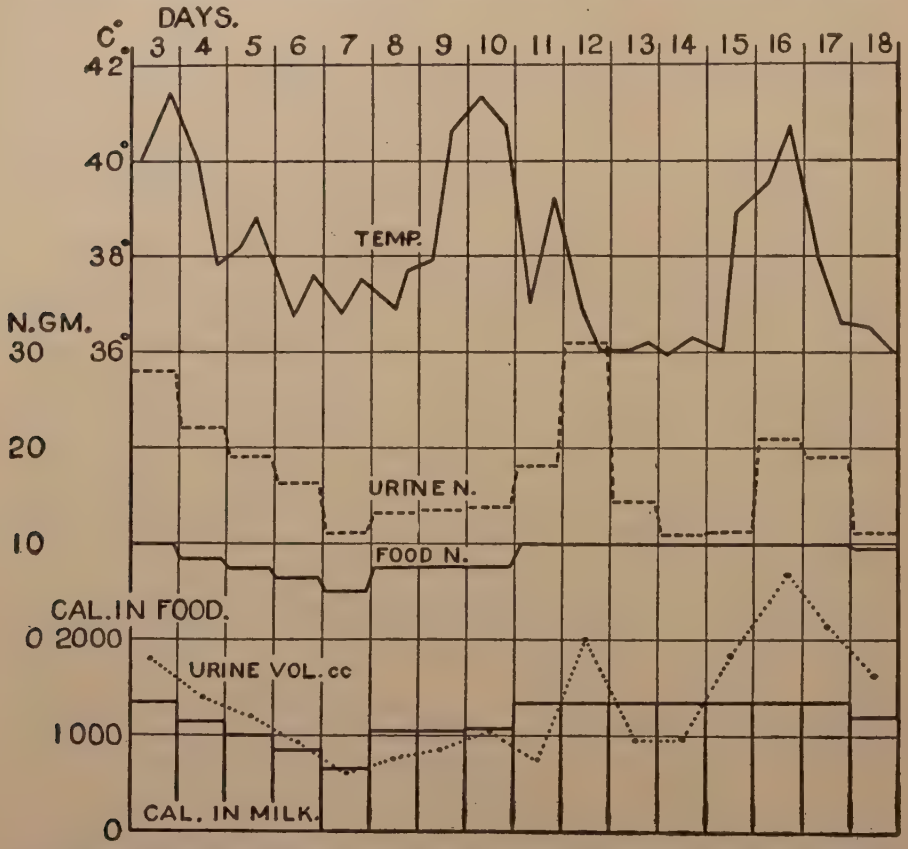

Fig. 24. Erysipelas patient studied by Loening. The patient was first taken ill with facial erysipelas on April 20th and did not become fever-free until April 27th. On April 30th he had a relapse. This metabolism experiment began on May 3rd. The diet consisted exclusively of milk. Note that the nitrogen excretion curve followed the temperature in the first and third relapses but showed a considerable lag or epicritical rise in the second relapse.

of the disease reached 2.4-2.6 gm. per day, the uric acid 0.8-2.0, and the ammonia 1.8-3.0. Mohr has found that the C/N ratio in the urine is within the normal limits in erysipelas as in other fevers.

Metabolism in Malarial Fever

Total Metabolism.—It is difficult to give figures which will represent the total caloric output of a patient with malaria since the heat production which is practically normal during the afebrile periods may be 200 per cent above normal during the chills. Numerous studies of the heat

production have been made by investigators who have attempted to find out the pathological physiology of temperature regulation. Liebermeister(*a*) studied the carbon dioxid elimination in 1871 and ascertained the more important facts by this simple method. Isaac Ott(*b*), of Philadelphia, made the first calorimetric measurements and Likhatscheff and Avoroff, of St. Petersburg, studied a malaria patient in the large Paschutin calorimeter. Recently Barr and Du Bois have reported results obtained on five patients studied in the Sage calorimeter. Between paroxysms and shortly before chills the average heat production of their patients was 14 per cent above the normal and the range was between 9 and 22 per cent above normal. After treatment with quinin and a return to normal tem-

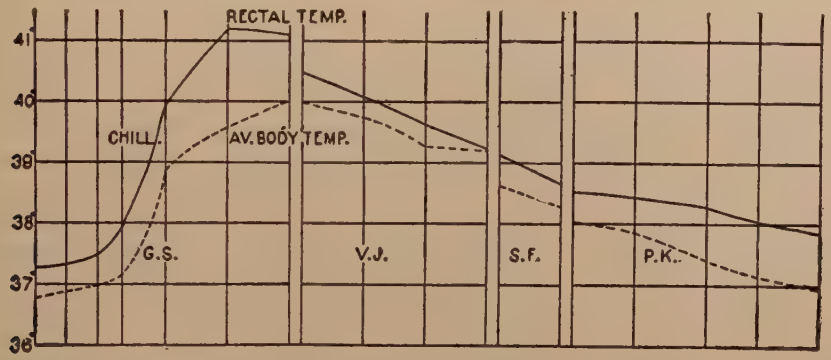

Fig. 25. Composite curve constructed from calorimeter observations on four patients in different stages of the malarial paroxysm. The continuous line shows the rectal temperature; the dash line indicates the changes in the average body temperature which, for purposes of calculation, is assumed to be one-half a degree lower than the rectal temperature at the start of each observation. (Taken from Barr and Du Bois.)

peratures two of the patients gave normal figures, the others were 10 and 14 per cent above the average. The daily expenditure for malarial patients of average size was estimated at 2,000-2,200 calories.

Temperature Regulation in Malaria.—Liebermeister found that the heat production was greatly increased during a malarial chill and that after the chill the temperature continued to rise although the heat production suddenly dropped to nearly its former level. Ott confirmed Liebermeister's findings and demonstrated the great increase in radiation, conduction and especially vaporization during the period of falling temperature when there was but slight change in the heat production. Likhatscheff and Avroroff added many details to the picture, and in general confirmed the earlier results. The work of Barr and Du Bois was done with a more accurate calorimeter which measured the oxygen consumption as well as carbon dioxid. Rectal temperature readings were made every four minutes and the experimental periods so adjusted that the metabolism could be measured just before, during and just after the chill. Heat pro-

duction was calculated from the oxygen consumption by the method of indirect calorimetry, the heat lost by vaporization and by radiation and conduction was measured by physical methods. Using Barr's method already described under typhoid fever they calculated the changes in the average body temperature and found that this curve was not always par-

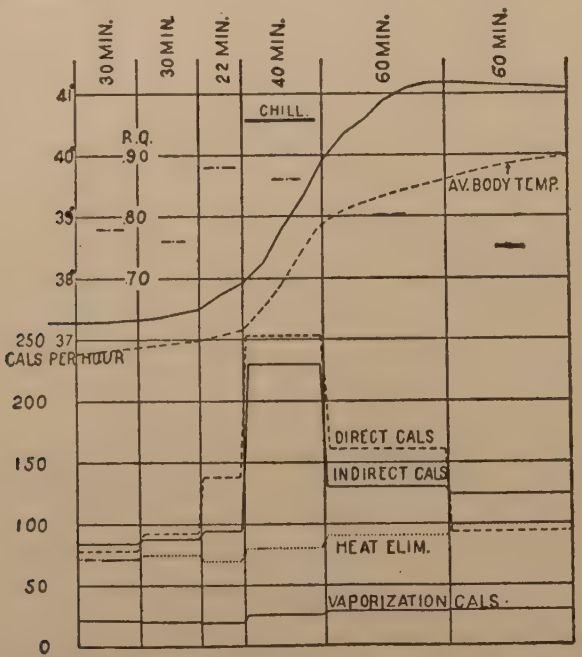

Fig. 26. Calorimeter observation made during the various stages of rising temperature. The continuous curve shows the rectal temperature, the dash line shows the changes in the average body temperature, starting arbitrarily at a point one-half degree below the rectal temperature. The level of the respiratory quotient is shown by the sign – · –. The lines below give the direct calorimetry (total heat production calculated from the heat elimination and the rectal temperature change), the indirect calorimetry (calculated from the oxygen consumption and respiratory quotient) and total heat elimination (vaporization plus the heat of radiation and conduction).

The patient was placed in the calorimeter about an hour and a half before the anticipated chill. By careful management it was possible to start the third period just before the rigor and end it about five minutes after the shivering ceased. Note the almost level metabolism before the chill, the enormous increase caused by the violent muscular action of the chill and the fall to a level higher than normal when the body temperature was still 41° C. (From Barr and Du Bois, Patient, G. S.)

allel to the change in rectal temperature. This is shown in Fig. 25, which is a composite of four different experiments. Fig. 26 shows the details of the phenomena of the rise in temperature as observed in one typical case. They summarize their results thus:

"The periods of malarial paroxysms may be divided as follows:

1. Preliminary. Temperature constant; no change in metabolism.
2. Prodromal. Fifteen or twenty minutes before the chill there is a slight rise in rectal temperature.

3. Chill. Rectal temperature rises abruptly; the surface of the body becomes relatively and perhaps actually cooler; the average body temperature rises somewhat less abruptly than the rectal temperature.
4. Rising Temperature after Chill. Rectal temperature rises less rapidly than during chill; the surface becomes warmer.
5. High, Continuous Temperature. Rectal temperature is constant; surface temperature rises steadily; patient feels hot.
6. Falling Temperature. Rectal temperature falls much more gradually than it rises. The surface temperature at first may continue to rise, then to fall gradually for a period, and later to fall at about the same rate as the rectal temperature.

The heat production increases 100 to 200 per cent during the chill; immediately after the chill it falls to within 20 to 38 per cent of the average basal level; with the falling temperature the heat production drops to normal.

During the period before the chill with constant temperature the heat elimination, of course, equals the heat production. During the chill, in spite of the enormous increase in heat production, the heat elimination is the same as in the preliminary period. Almost all of the extra heat produced is stored in the body tissues.

In the fourth period of rising temperature after the chill there is a slight increase in heat elimination. In the fifth period of continuous temperature heat elimination begins to equal heat production. In the sixth period of falling temperature the heat elimination is greatly increased, chiefly by means of a large increase in the vaporization of water from the skin. Of the total calories produced in this period the patient loses a much larger percentage than normal through vaporization. On the other hand, the percentage of calories lost through vaporization is not greatly increased in its relationship to the total heat elimination."

It is interesting to note that the phenomena of the malarial chill are duplicated almost exactly in the chills which follow the intravenous injection of proteose or foreign protein as has been shown in the unpublished work of Cecil, Barr and Du Bois, who used the same calorimeter in the study of this form of experimental fever.

Character of Foodstuffs Oxidized.—In the calorimeter experiments the respiratory quotients were all within normal limits, the highest being 0.88 and the lowest 0.72. There is an interesting rise in the quotient during the chill, as is shown in the dash dot lines in Fig. 26. Before the rise in temperature the patient was deriving about 17 per cent of the calories from carbohydrate. Just before the chill and during the chill the percentage rose to 58 and 52 per cent. After the chill the percentage dropped first to 27 and then to 16. It is quite possible that an "Auspumpung" of CO_2 due to hypernea at the beginning of the rigor makes the respiratory quotient a little too high and that a compensatory retention at the end of hypernea makes it a little too low, but it is safe to say that

carbohydrates furnish an increased proportion of calories for the muscular work of the chill just as they do for other muscular exercise.

The destruction of body protein does not seem to be as great in malaria as in the continued fevers. Sharpe and Simon in a recent study of transient fevers have found during the rise of temperature a tendency for a rise of urinary nitrogen and less uniformly of creatinin. Three of the patients studied by Barr and Du Bois showed negative nitrogen balances when they were receiving in their food more calories than they required to cover the heat production as determined by calorimetric tests. This points towards a toxic destruction of protein, but variations in the kidney function may obscure the true protein metabolism.

Direct and Indirect Calorimetry.—Litkatscheff and Avroroff did not compare the heat production as determined by the method of indirect calorimetry with the results obtained by the direct method but from their data it is possible to make the calculation. On the day of normal temperature the direct method was 6 per cent higher than the indirect, on the two febrile days 6 and 12 per cent lower. This is good agreement when one considers the difficulties of their methods. With the Sage calorimeter the agreement was usually good when all the experiments were taken together the total divergence being less than one tenth of one per cent. In the febrile periods alone the total divergence was 0.7 per cent, but in some of the individual periods with great body temperature changes the differences were enormous, as is the case in all fevers.

Chlorids and Phosphates in Malaria.—Malarial fever occupies an anomalous position in regard to the excretion of chlorids and phosphates. In almost all other fevers there is a marked decrease in the excretion of chlorids, usually accompanied by an increase in the excretion of phosphates. It has been shown that the blood chlorids are decreased in pneumonia so that the disturbance does not seem to be due to the kidneys but to a retention in the tissues. In malaria, on the other hand, Terray, Bookman and numerous other investigators have shown that the chlorid excretion is greatly increased during the febrile attacks and decreased in the intervals of normal temperature. The curve for phosphates shows a decrease during fever and a rise in the intervals. It would be interesting to follow the curves for these substances in the blood and study the kidney function.

Fever Caused by the Parenteral Injection of Foreign Proteins

It is hardly within the scope of this article to discuss fully the question of the parenteral injection of foreign proteins, as this would lead too far

into the realms of immunology. Some of the experimental work, however, has been along metabolic lines and has supplemented the findings in the ordinary infectious diseases. The matter is not unimportant from a clinical standpoint since the intravenous administration of vaccines is now used in many clinics.

The history of the early clinical applications has been well reviewed by Jobling and Peterson(*b*), who describe the pioneer work of Matthes(*a*), Fraenkel and others. Miller and Lusk(*a*)(*b*), Gay and Chickering, Cecil,

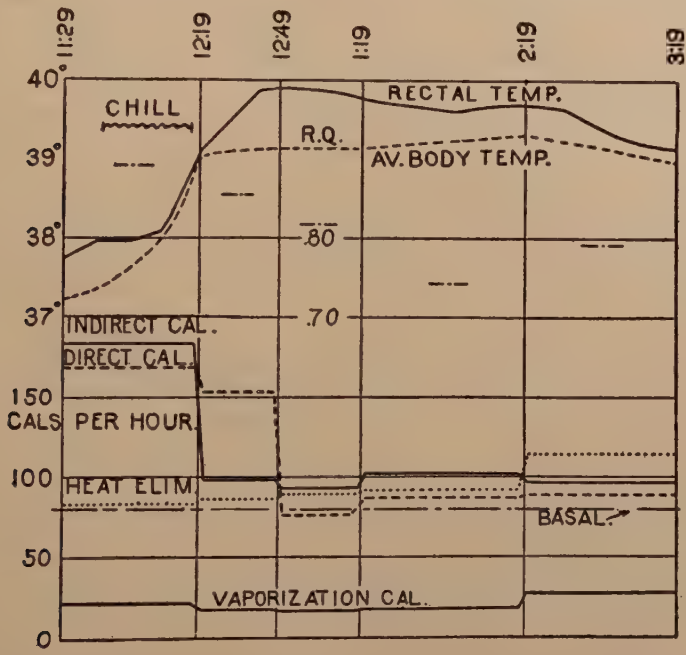

Fig. 27. Calorimeter observation of chill following the intravenous injection of 25 million killed typhoid bacilli. The subject, a young man of 19 years, suffered from gonorrheal arthritis. The injection was made at 10:50 A.M. and the observation started at 11:29 A.M. Note the similarity between this chart and the ones showing the malarial paroxysms.

Snyder and numerous other clinicians have tried foreign proteins, proteoses, etc., intravenously in many diseases. The results have been somewhat encouraging, especially in chronic arthritis, but at the present time the method is not in great vogue. Accidents have occurred, but those who are experienced in its use say that it is harmless if proper precautions are observed.

When a patient is given intravenously a small dose of foreign protein, say 20 to 50 million killed typhoid bacilli, the clinical phenomena are striking. After a latent period of a few minutes the patient is suddenly seized with a violent chill resembling in every respect a malarial paroxysm.

The temperature rises abruptly, remains high for a few hours and then falls more slowly than it rose. The phenomena of this period of fever have been studied in some detail by Jobling and Peterson, Miller and Lusk, Scully and others. There is a primary leukopenia followed by a marked leucocytosis, a primary lessening of the coagulability of the blood followed by reduction of the coagulation time. The flow of lymph is increased greatly and there is hyperperistalsis of the intestinal tract. Serum protease and lipase are increased and there are changes in the antiferment titer. A rise in nitrogen excretion has been found in animals after parenteral injection of foreign proteins by Friedmann and Isaac, Vaughan,

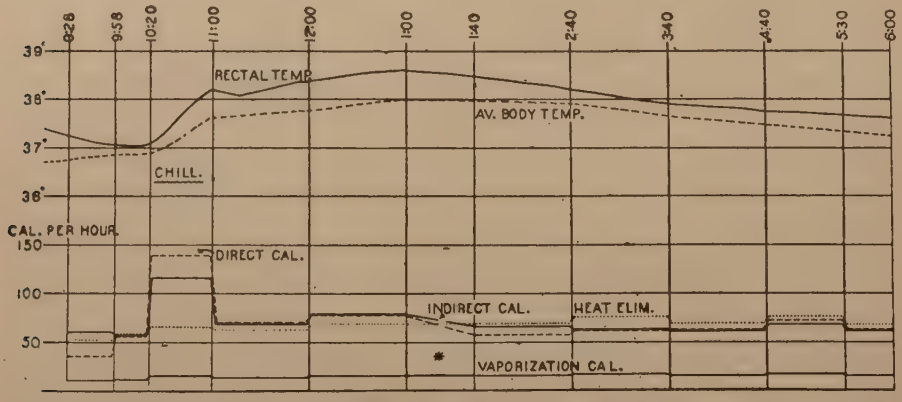

Fig. 28. Patient 27 years old with gonorrheal arthritis given 50 million killed typhoid bacilli intravenously at 9:05 P.M. Observation started at 9:28 P.M. and continued throughout the night with one short interruption from 1 A.M. to 1:40 A.M. Note the sharp rise of the rectal temperature and the more gradual changes in the average body temperature. The heat elimination rises above the heat production at the time that the body temperature falls. Direct and indirect calorimetry agree closely in all periods after the chill.

Schittenhelm and Weichardt, Major and many others. Whipple and Cooke found the greatest increase in 24-48 hours after injection and then a gradual decline over 3-5 days. Hirsch(*b*) did not find a constant increase in the heat production of rabbits during anaphylotoxin fever although she did obtain it in the fever of trypanosomiasis and heat puncture.

After the subcutaneous administration of large doses of vaccine the clinical phenomena are similar though not so dramatic. In such conditions Leathes(*b*) and later Sharpe and Simon have demonstrated a rise in the excretion of nitrogen, uric acid and creatinin.

The onset of the chill following the intravenous administration of vaccine can be so accurately regulated and timed that it furnishes an ideal opportunity to study the matter of the regulation of body temperature. Barr, Cecil and Du Bois studied a number of patients in the calorimeter during the various phases of the paroxysm. Figures 27 and 28 taken from

their work show the same curves that were observed in malarial fever. There is the same enormous increase in heat production during the chill and gradual increase in heat elimination during the fall and the same lag in the change of the average body temperature as compared with the rectal temperature.

Cholera

Asiatic cholera differs from other fevers in its profuse diarrhea, which is accompanied by a striking dehydration of the tissues and diminution of the urinary secretion. Acute nephritis with anuria is not uncommon, and the clinical picture of uremia is often encountered. Sellards and Shaklee have found a marked resemblance between the metabolism in this uremic stage and diabetic coma. In the first place the cholera patients show a high tolerance for alkalis and take as much as 90 gm. of sodium bicarbonate before the urine becomes alkaline. Normal controls show an alkaline urine after 5 to 10 grams. The ammonia in the urine is increased both relatively and absolutely. There is a definite reduction of the CO_2 in the blood and the tests indicated a diminished alkalinity of the blood. They found some acetone and diacetic acid in the urine, but not enough beta-oxybutyric acid to be compared with diabetes. Good results were obtained therapeutically by the use of alkalis, and, if administered early enough, they seemed to prevent the uremia.

Rogers studied the salt metabolism in cholera and found that the "rice water" stools contained, on an average, 0.53 per cent of chlorids. In the blood serum the average content was 0.79 per cent, sometimes being as low as 0.6 per cent. Recovering cases had chlorids slightly above the normal. It was obvious that the body was losing large amounts of sodium chlorid on account of the diarrhea and the replacement of this by means of hypertonic salt injections was found to improve the condition of the patients. Valk and deLangen, working in Batavia, found that the urea of the blood was between 60 and 590 mgm. per 100 c.c., with an average of 350 mgm. These figures are astonishingly high, high even for uremia.

It is somewhat difficult to determine just which pathological factors account for the various abnormalities above described. The kidney lesion could explain the high blood urea and perhaps the high tolerance for alkalis and other signs of acidosis. On the other hand, the dehydration of the tissues may be a factor in producing these and in producing the nephritis.

It seems safe to assume a great concentration of the blood. In the presence of all of these complications there is no way of finding out just how much is due to the toxin of the cholera itself.

Miscellaneous Infectious Diseases of Man

Syphilis.—There are few infectious diseases of more importance than syphilis, yet the studies of the metabolism in this condition are surprisingly scant. The comparatively slight constitutional effects and the chronicity of the disease have probably led investigators to believe that the abnormalities in metabolism were so small as to be negligible. The early work of Jakovleff and of Radaeli indicated an increase in the nitrogen losses during the period of the initial lesion and later during the generalized eruption with some diminution of the absorption of protein by the intestines. Their experiments were made with such large protein rations that the changes in nitrogen output are not conclusive.

We are indebted to a young Finnish dermatologist, Cedarkreutz, for an excellent piece of work done in 1902. He used Landergren's method of specific nitrogen hunger about twelve years before its adoption in other medical clinics as one of the best methods of determining small changes in the nitrogen metabolism. This diet contained practically no protein but plenty of fats and carbohydrates to cover the patient's requirement. After four days of this ration the normal controls were excreting 3.4 to 4.0 gm. of nitrogen per day. One syphilitic patient with a secondary eruption excreted 4.9 and 4.5 gm. N. One woman with roseola, who had slight fever on the first two days of the diet, did not fall below 7.3 gm. Five experiments on other patients with early syphilis gave normal results. He found that mercury and potassium iodid had no effect on normals and that the relationship of urea and uric acid excretion was normal in all the syphilitics. On the whole, the findings of Cedarkreutz indicate that there is little toxic destruction of protein in early syphilis, although one of his patients with fever showed that it may be present.

The work of Tileston and Comfort and of Schwartz and McGill indicates that most patients with syphilis have little or no increase in the blood urea but that some, particularly in the tertiary stage, have figures considerably above the normal. Gorham and Meyers found the cholesterol content of the blood about the same in syphilitics as in their normal controls. In tuberculosis and typhoid fever there was a considerable increase.

Scarlet Fever.—In scarlet fever Pipping found that the nitrogen excretion was abnormally high in most of his cases but he was able to bring one patient into nitrogen balance on a very liberal diet. Loening observed that the nitrogen excretion remained high for 8 to 10 days after the drop in temperature but did not believe that this was due to kidney insufficiency in spite of the fact that many of his patients suffered from nephritis. Tileston and Comfort, in four mild cases of this disease, were not able to establish a retention of non-protein nitrogen in the blood, but

Veeder and Johnston obtained figures for non-protein nitrogen and creatinin which were slightly above normal.

Oppenheimer and Reiss demonstrated a considerable retention of sodium chlorid in scarlet fever. In one case with 6 gm. in the food there was only half a gram in the urine. During this period of positive salt balance there was an increase in body weight and a diminution in the concentration of protein in the blood, indicating a retention of water in the blood. When the fever disappeared the weight dropped and the concentration of protein in the blood rose to normal. Magnus-Alsleben made some interesting studies on the acid excretion in scarlet fever, finding large amounts of organic acid in the urine. Mohr, who has studied the C/N ratio in scarlet and other fevers found the ratios, on the whole, were normal.

Acute Rheumatic Fever.—Comparatively few studies have been made of the metabolism in acute rheumatic fever. Rolland was able to attain nitrogen balance in one patient when she administered daily in the food 11.5 grams of nitrogen and 3,400 calories (56 calories per kilogram). This was undoubtedly greatly in excess of the patient's heat production. Kocher gave a 16-year-old patient weighing 35 kilograms 2,600 calories per day (77 calories per kilogram) with 0.96 to 1.12 grams of nitrogen in order to determine the nitrogen minimum. The nitrogen output in the urine remained over 11 grams a day until the fever was ended, when a normal figure of 3.2 grams was reached. The creatinin was 1.6 to 1.8 grams and the uric acid 0.8 to 1.3 grams a day. These experiments of Rolland and Kocher show exactly the same phenomena as in typhoid fever and point towards a toxic destruction of protein. Frothingham, in a series of rheumatic fever patients, found a few with some evidences of acidosis and a few with a low excretion of phenolsulphonephthalein. Freund and Marchand, in nine cases, obtained an average blood glucose of 116 mgm. per 100 c.c.

The first accurate calorimetric observations on the metabolism in fever were made by Carpenter and Benedict(*b*) in the large Atwater-Rosa-Benedict calorimeter in Middletown, Connecticut. While they were making experiments on normal men a number of their subjects developed fever with symptoms of malaise and nausea. The cause of the disturbance was never absolutely certain, but it seemed to be a form of poisoning from mercury used to seal the air valves, and a removal of this mercury put an end to the febrile attacks. The same subjects were observed later without fever, and it was evident that during the periods of high temperature there was a distinct increase in the oxygen consumption, and carbon dioxid and water elimination. Since the experiments were made during the period of rising temperature the increase in heat production was more marked than the increase in elimination.

It is interesting to compare the metabolism in toxic fevers with that

in non-toxic hyperthermias produced by warming men in hot water baths or steam. Rubner found that there was a distinct increase in the metabolism when subjects were placed in a bath at 44° C. Schapels obtained similar results. Graham and Poulton, using a vapor bath, were able to raise their body temperatures to 39.3° and 40.2° for a short time without increasing the nitrogen output which had been brought down to the nitrogen minimum of 3 to 4 grams per day. This indicated that a short non-toxic fever causes no abnormal destruction of protein in a patient receiving an abundant supply of fat and carbohydrate in the food. Linser and Schmidt studied several patients suffering from acne and two brothers with ichthyosis. These latter could not cool their bodies by sweating and therefore developed high temperatures readily when the room was warmed. There was no increase in the nitrogen elimination unless the body temperature was raised above 39° to 40° C., in which case there was an increase of 2 to 3 grams per day.

Experimental Fever in Animals

There is a vast literature dealing with the production of fever in animals. Most of it is foreign to a paper which deals with the metabolism in the infectious diseases of man and belongs either to the realms of physiology or immunology. Some of it deals with metabolism in conditions which resemble the diseases of man and interests us for this reason. On the whole, the experimental work on animals is full of contradictions and controls are scanty in almost all the papers. At the present time we are realizing more and more fully the necessity of a large number of controls in all experiments and are discovering the wide range of normals in the species most carefully studied. At the present time there are comparatively few experiments on the metabolism of animals with fever that have not been duplicated on man.

We are fortunate in possessing several excellent reviews of this subject. Tigerstedt, Richter and more recently Lusk have dealt with the literature in a manner which makes it unnecessary to do more than mention some of the more recent work.

The whole question of the heat centers in the brain is in great confusion as a result of the work of Jacobj and Roemer and of Lillian Moore(*a*)(*b*). All of these investigators deny the existence of a special heat center. Jacobj and Roemer produced rises in temperature by irritation of the ventricles of the brain by carbolic acid or mercury with resulting hydrops and dilatation. Lillian Moore, working with rabbits, found a large range in the temperature of normal rabbits and obtained striking changes in temperature by tying down the animals, by anesthesia and by trephining the skull. Often these variations were as great as those reported

as due to puncture of the "heat center." She also obtained hyperthermia whenever there was an increase in the intracranial pressure.

Much of the earlier work on "salt fever," "water-fever" and the other fevers which follow the injection of various substances dissolved in water must be reviewed in the light of the more recent work which shows that these reactions were due to some unknown fever producing substance which is present in water unless it has been freshly distilled. Hort and Penfold and many others have called attention to this experimental error. Stokes and Busman have discovered another source of fever in certain impurities in "pure gum" tubing. This toxic substance is dissolved by alkaline solutions such as are used in the administration of salvarsan.

We are indebted to Flury and Groll for some exceedingly interesting studies on the metabolism in animals with trichinosis. They found that the trichinæ enter the muscles because they need carbohydrate for their metabolism, and once established there abstract glycogen and live anoxybiotically. They secrete end products among which are free fatty acids causing certain changes in the muscles. There is a diminution in the muscle fibers, total nitrogen, glycogen, purin bases and creatin. Extracts of trichinous muscle are much more poisonous than normal extracts and cause vomiting, diarrhea, fever and an edema which is probably due to a capillary poison. Flury was able to produce practically every sign and symptom of trichinosis by using muscle extracts which contained no living organisms.

In conclusion we shall direct our attention to the stimulating work of Balcar, Sansum and Woodyatt, who produced extraordinarily high temperatures in dogs by giving concentrated solutions of salt, lactose or glucose intravenously. As the strong glucose solution was continuously pumped into the vein there were a diuresis and marked diminution of the water content of the body. Later there was a severe chill with rise of temperature, convulsions, anuria and death. Temperatures as high as 109°-111° F. were frequently obtained and on one occasion the thermometer recorded the unprecedented figure of 125.6° F. (52° C.). Woodyatt believes that this is due to a diminution of the free water in the body caused by diuresis and by a combination of water with the glucose or salt injected. With such a diminution of the water reserve it is impossible for the body to transport to the surface and there dissipate by vaporization the heat constantly generated in the tissues. This explanation is quite applicable to the dehydration fevers of infants formerly spoken of as "inanition fever" or "salt fever" or "sugar fever." At the present time it seems doubtful if it can help us greatly in the explanation of the fever of infectious diseases.

Edema . . . . . *Franklin C. McLean*

Introduction—Definition—Historical—The Problem of Edema—The Clinical Features of Various Forms of Edema—The General Features of Edema—Special Forms of Edema—The Morphology and Chemical Pathology of Edema—Morbid Anatomy—The Chemistry of Edema Fluids—The Pathological Physiology of Edema—Definition of Terms—Disturbances in the Flow of Lymph—Cell Metabolism and Edema—Cell Respiration and Edema—Protein Metabolism and Edema—Inorganic Metabolism and Edema—The Rôle of the Thyroid in Edema—Capillary Permeability and Edema—Circulatory Changes and Edema—Rate and Volume of Blood Flow—Blood and Plasma Volume in Edema—Composition of the Blood in Heart Failure—Renal Function in Its Relation to Edema—Chronic Interstitial Nephritis—Acute Diffuse Nephritis—Subacute and Chronic Diffuse Nephritis—Chronic Parenchymatous Nephritis—Renal Function in Other Conditions Associated with Edema—Summary—Lymph Production and Edema from the Physico-Chemical Standpoint—The Production of Lymph—The Nature of Edema—Physico-Chemical Factors in Lymph Production and Edema—Hydrostatic Pressure—Diffusion Pressure—Hydrophilic Action of Colloids—Electrostatic Pressure—Influence of Chlorids and Fluids—The Treatment of Edema—Prophylaxis—Etiologic Treatment—Dietetic Treatment of Edema—Drug Therapy.

Edema

FRANKLIN C. McLEAN

PEKING

Introduction

Definition.—Edema is a local or general condition, characterized by the presence of abnormally large amounts of fluid outside of the vascular system. The fluid resembles normal lymph in composition, and is usually found in the intercellular spaces or serous cavities, but an increase in the intracellular fluids may also occur. The condition results from a derangement of the function which has to do with the continuous exchange of fluids between the blood and tissues, and with the regulation of the volume of the tissues.

Historical.—The clinical occurrence of edema and its relation to a diminished output of urine have been recognized since the time of Hippocrates, but it is only within the last century that any accurate knowledge concerning the condition, in its relation to the disturbances which cause it, has been accumulated. Especially within the past thirty years an enormous literature on the subject has become available, and much progress has been made towards arriving at a more complete understanding of the various factors concerning its pathology.

The present knowledge of the mechanism of the occurrence of edema, and even of the process of normal lymph production, is far from satisfactory, in spite of the progress which has been made. Certain fundamental problems, such as the relation of the excretory function of the kidneys to edema, are still unsolved. It is necessary, therefore, to treat the whole subject of edema as a problem, the final solution of which has not yet been reached. It is of interest to review the historical development of this problem, especially with reference to the trend of thought relating to it.

Bright(*a*), in 1827, recognized the association of edema with disease of the kidneys, manifested clinically by albuminuria, and at autopsy by definite pathological changes in these organs. He also recognized the occurrence of a diminished protein content in the blood serum and suggested the probability of a disturbance in the healthy balance of the

circulation. His observations as to the diminished protein content, with subsequent lowering of the specific gravity of the serum, were confirmed by numerous observers, and for some years the impression was current that there was, in effect, an hydremia, due to the loss of albumin through the urine, and that this resulted in increased transudation of fluid from the capillaries into the tissues.

Stewart (1871) and Bartels (1875), while recognizing the possibility of such an effect of loss of albumin, called attention to the parallel between diminished output of urine and the occurrence of edema, a phenomenon which, in fact, had been recognized by Hippocrates. Both of these authors observed that edema might occur before there had been any significant loss in albumin from the blood serum, and that there was a marked disturbance, in all cases, in the normal balance between daily fluid intake and output. They concluded that the kidneys, by failing to excrete water, caused its retention in the body; this water tending to dilute the blood and resulting, by transudation, in edema.

Cohnheim and Lichtheim (1877) injected large amounts of physiological salt sodium intravenously into rabbits, and found that amounts up to 92 per cent of the body weight could be injected without causing edema, and that edema only occurred when the capillaries were injured. They concluded that both hydremic plethora and injury to the capillary walls were essential to the production of edema.

Senator(*e*)(1895) believed that poisonous substances circulating in the blood injured first the glomeruli and later the capillary endothelium, and that such toxic action produced the conditions regarded by Cohnheim and Lichtheim as necessary for edema to occur.

Magnus(*a*)(1899) offered further experimental evidence in support of the conclusions of Cohnheim and Lichtheim. He found that edema could not be produced in animals by an artificially produced hydremic plethora, unless the capillaries had previously been injured by such poisons as arsenic, chloroform, chloral hydrate, or phosphorus. Similarly, Richter(*d*)(1905) produced edema in rabbits by injections of uranium nitrate, which effect he attributed to injury to the capillaries.

Landerer (1884) introduced another point of view. His conception of the process was that edema was due to faulty nutrition of the tissues, resulting in a loss of their normal elasticity, and a consequent infiltration of fluid into them.

Lazarus-Barlow(*a*)(*b*)(1895) also regarded edema as due to a primary disturbance in the tissues, an abnormal metabolism resulting in the breaking down of large molecules into smaller ones and an increase in osmotic pressure in the tissues, with a consequent withdrawal of fluid from the capillaries. Loeb(*a*)(1898) also believed that there was an increased osmotic pressure in the tissues, and attributed it to acid formation, due to diminished oxygen supply.

Fischer(*a*)(1910), on the basis of experiments with the swelling of frog's muscle, supported the view that the cause of edema lies in the tissues, and concluded that it is due to swelling of the colloids of the tissues, as a result of increased acid production.

Achard and Loeper (1901) called attention to the importance of sodium chlorid in the maintenance of the balance of fluid between the blood and tissues, and concluded that the tissues were injured by substances retained by the kidneys, the result being a withdrawal of salt from the blood by the injured tissues.

Widal (1903), in his classical experiments with Lemierre and with Javal, showed that edema could be produced and made to disappear at will, in certain cases at least, by varying the salt intake of patients.

Strauss(*c*)(*d*)(1903) also called attention to the importance of the retention of sodium chlorid, explaining edema on the basis of insufficient excretion of salt, resulting in the retention of water, due to increased osmotic pressure.

Epstein(*b*)(1917) has concluded, as did the followers of Bright, that the primary cause of edema is the diminution of the protein content of the blood, due to the loss of protein through the kidneys.

The Problem of Edema.—Whatever may be the primary cause of edema, whether it is renal insufficiency, with respect to the elimination of water or of salt, or the loss of protein from the blood, or injury to the capillaries, by mechanical or chemical causes, or a disturbance in the metabolism of the tissue cells, the problem of edema is the problem of the interchange of fluid, with its dissolved and suspended substances, between the blood and the tissues. As this interchange of fluid is concerned with the nutrition of the cells, the carrying off of products of cell metabolism, and the regulation of volume of the cells, the problem is ultimately that of cell metabolism. For a perfect understanding of the process of fluid exchange between the blood and the tissues, it is necessary to have a picture more clear than is available of the interrelations of the various physical, chemical, and physico-chemical processes which are involved. It is at present desirable to analyze, as fully as possible in the light of present knowledge, the mechanism underlying this process, especially under the abnormal conditions associated with edema.

For this purpose this discussion is limited, as far as possible, to the general aspects of edema, avoiding extensive description of special types. The clinical, pathological, and experimental features of the condition are considered first objectively. There follows an analysis of the mechanism from the physico-chemical viewpoint, and a discussion of the special treatment, insofar as it relates to the pathology of metabolism. The purely local effusions, such as hydrocele, and the inflammatory exudations are not discussed, except insofar as they throw light on the general problem of edema.

PART I

The Clinical Features of Various Forms of Edema

The General Features of Edema.—The recognition of edema is usually not difficult, especially in the subcutaneous tissues, where, as a rule, it first appears. The edema of heart failure, which appears first in the most dependent portions of the body, and the edema of nephritis, which shows a particular predilection for the soft tissues about the orbit, are familiar to every physician.

The Skin and Subcutaneous Tissues.—In the early stages of edema the skin may appear normal, on mere inspection, especially in cases of heart failure during the stage when the edema disappears at night. The first objective sign is usually the characteristic pitting on pressure. If edema is present, when firm pressure is made with the finger tips the depression produced remains after the finger tips are removed, and may be observed by inspection or by passing the fingers lightly over the area. When no edema is present the normal elasticity of the subcutaneous tissues restores the contour of the skin as soon as the finger tips are removed. Ordinarily such pressure over an edematous area causes no pain.

A slight puffiness about the eyes is frequently the earliest sign of the edema of nephritis. Here the tissues are too soft to elicit pitting on pressure, but the puffiness, often associated with a pasty appearance of the skin, is characteristic.

After edema has persisted for some time the skin assumes a thin and transparent appearance. As it increases, it becomes smooth and shiny. At first, soft and pitting easily on pressure, the edematous tissues later become hard and indurated. Considerable pressure may then be necessary to cause pitting. This is especially true of edema of heart disease, if the patient has not been confined to bed, but the forms of edema which occur independently of circulatory disturbance are less influenced by posture.

The edema of heart failure nearly always shows the influence of gravity, in that the more dependent portions of the body are involved first. When there is a considerable amount of fluid in the extremities, accompanied by marked distentions of the skin, trophic changes may result from the disturbance of nutrition. Blebs and bullæ are not uncommon, and occur most frequently on the feet and legs. Occasionally the skin breaks and there is leakage of watery fluid through the fissures. Secondary infection of such lesions may result in changes due to inflammation.

Inflammation of the skin or subcutaneous tissues often leads to more or less circumscribed areas of edematous swelling about the point of infection. Here the swelling has the characteristics of edema, in combination with those of inflammation.

Hydrothorax and Ascites.—Associated with the formation of edema in the skin occurs the development of similar processes in the body cavities. Especially common are hydrothorax and ascites. In fact, either may occur early and become a prominent factor in the condition of the patient when there is little or no subcutaneous edema.

In heart failure hydrothorax occurs most frequently on the right side, although it is often bilateral. This preponderance is variously attributed either to the habit of most persons, especially those with heart disease, of lying on the right side, or to pressure of a distended right heart on the azygos veins of that side. In other cases there is a disposition to ascites, due probably to pressure on the veins of the abdominal cavity.

The Liver.—Edematous swelling of the liver and other internal organs is especially common in heart disease. The enlargement of the liver commonly seen in heart failure is in part a result of edema of that organ, and in part a result of distention due to passive congestion.

The Kidneys.—Some of the changes in the character and amount of the urine excreted in the course of passive congestion may be due to involvement of the kidneys by edema. Such changes in the urine, however, are due in part directly to the diminished rate and volume of blood flow through the kidneys, and in part to the effect of changes in the physicochemical constitution of the blood.

The Lungs.—Slight edema of the lungs is often one of the earliest manifestations of heart failure. This occurs usually at the base of the lungs, and may be detected on auscultation by the presence of fine moist râles on deep inspiration.

In the later and graver forms of heart failure the disturbance may become severe, until finally pronounced pulmonary edema occurs. When this takes place there is a sudden outpouring of fluid into the alveoli, with consequent expectoration of large amounts of frothy, blood-stained fluid. Relief from this condition may occur either promptly or after the lapse of varying lengths of time. In some instances there is only one attack, but in others, recurring pulmonary edema is a prominent feature of the disease. Such an attack may be the terminal event.

Edema of the lungs, as well as of other internal organs, is less common in association with edema due to other causes than to circulatory failure. It may occur from local irritation of the lungs from poisonous gases, and is not uncommon as a complication of lobar pneumonia.

Special Forms of Edema.—The general manifestations of the various forms of edema are similar. There are, however, certain points relating to the occurrence of these forms and to their clinical features, to which attention must be called. For this purpose it is convenient to adopt an etiological classification of the forms which are to be discussed.

Edema from *mechanical causes* is typified in the edema of heart failure, in which the *disturbance in rate and volume of blood flow* seems

to be the underlying cause. In this form the association of edema with other symptoms of heart failure, and the influence of gravity on the location of edema, are the prominent features. Local edemas, from mechanical causes, are common, and may be due to direct injury to the tissues, by trauma or inflammation, or to interference with the venous or lymphatic flow from an organ or region of the body. *Ascites,* in cirrhosis of the liver, is associated with obstruction to the portal circulation. Other local edemas may be due to venous obstruction, caused by pressure, thrombosis, or trauma, or they may be due to blocking of the lymph channels by parasites (Filaria), or by trauma. *Glaucoma* is usually attributed to mechanical obstruction to the lymph return from the anterior chamber of the eye.

Edema from *chemical causes* includes the edema of nephritis, in those cases in which edema is not due to circulatory failure. It also includes the so-called *soda-edema.* This form follows the administration of large doses of sodium bicarbonate in certain conditions in which there is already an abnormal metabolism, as, for instance, in diabetes or cachexia. Spontaneous edema is also common in *cachexia* or *inanition,* especially in infants or in the aged. Such cases have occurred in large numbers during the past few years, especially in communities where there were enforced dietary restrictions. This condition has been variously known as *war-edema, "oedemkrankheit,"* and *famine-edema.* It appears to be due to a *dietary deficiency,* and especially to a *diminished protein intake,* continued over long periods of time.

Protein poisoning is now commonly recognized as a cause of edema. It usually assumes either the form of *urticaria,* which is more or less limited to the skin, or of the condition known as *angioneurotic edema,* which is similar to urticaria, but involves the subcutaneous tissues as well and may in addition involve the mucous membranes. The latter is also associated with certain general manifestations and with disturbances in metabolism (Miller and Pepper). These conditions may follow the oral or subcutaneous or intravenous administration of foreign products. Edema then occurs only in individuals sensitive to particular proteins, and edema is a part of the general phenomenon of anaphylaxis. Individual sensitiveness to a large number of foreign proteins has been found in otherwise normal individuals. Unexplained urticaria and angioneurotic edema are usually attributed to food poisoning. They have a tendency to recur.

Neuropathic edema may be associated either with functional or anatomical nervous disorders. It has been observed after section of a peripheral nerve, and in transverse myelitis, syringomyelia, poliomyelitis, and cerebral lesions. Although it has by no means been demonstrated, it is generally assumed that this form of edema is due to vasomotor disturbances. Hertz and De Jong have found renal disturbances in certain cases with neuropathic edema, and state that in the majority of cases the

nerve lesion in itself is *not sufficient* to cause edema, but that a localized edema may follow a nerve lesion provided there is a coincident disturbance of renal excretory function predisposed to edema. Certain cases of *paroxysmal edema,* such as have been reported by Palmer(*b*), occur periodically and sometimes without evidence that any of the general conditions usually associated with edema is present. These cases are probably due to functional nervous disorders.

Milroy (1892) described a form of chronic *hereditary edema* affecting a large proportion of the descendants of the first individual known to have had the condition. Since then similar instances of familial edema have been described by various authors (for literature, see Hope and French). The edema is usually restricted to the legs. The individuals affected are usually otherwise healthy and, unless incapacitated by the swelling of the extremities, lead long, active lives. It may be present at birth, but more commonly appears at the age of puberty, the time of appearance being also a familial characteristic, and lasts throughout the life of the individual. It occurs in, and is transmitted through, both males and females. In certain cases, in addition to the chronic swelling, there are acute exacerbations of increased swelling during which the swollen areas are red and painful. Constitutional symptoms resembling those of angioneurotic edema appear at this time. There is no traceable cause for the occurrence of this condition.

Inflammatory edema is generally localized about the point of inflammation, and is apparently due to both mechanical and chemical causes.

PART II

The Morphology and Chemical Pathology of Edema

Morbid Anatomy.—The accumulation of fluid in the tissues of the body, with the clinical characteristics of edema, is as a rule intercellular rather than intracellular. Intracellular accumulations do occur, under normal as well as under abnormal circumstances, since the cells serve as reservoirs for fluid, but a pathological accumulation of fluid is not generally recognized as edema until the intercellular fluid increases. It is the spreading apart of the tissue cells by intercellular fluids which gives to the tissues the characteristic loss of elasticity.

At autopsy fluid is found in varying amounts in the subcutaneous tissues and in the body cavities, usually where it has been demonstrated clinically. In some chronic cases the fibrous elements of the skin are thickened, forming brawny edema, or induration of the skin. In other cases patches of the superficial layers of the epidermis are raised in blebs or large bullæ. When the skin has actually broken down and secondary

infection has occurred, evidence of inflammation is added to the picture of edema.

The edematous tissues are swollen, permit fluid to escape on incision, and are inelastic, retaining the impress of one's fingers on pressure. This condition may be observed in the organs at autopsy, but it is generally most striking in the subcutaneous tissues. The edematous organs or tissues are found to have lost much of their opacity, and may appear almost agate-like. This is seen especially in the lungs and in fibrous and muscular tissues, such as the walls of the intestines and gall-bladder, the pelvis of the kidneys, and the subcutaneous tissues in general.

Microscopically there may be seen clear spaces in or between the cells of the organs. In cases of long standing there may be evidence of secondary retrogressive changes.

The Chemistry of Edema Fluids.—Edema fluids, when non-inflammatory in origin, are known as transudates. They vary in composition in different parts of the body, and in different conditions, but in general they resemble the composition of the blood plasma of the same individual, with the exception that they are much poorer in proteins. The specific gravity, which varies directly with the protein content, is usually below 1.015. Exudates, or fluids of inflammatory origin, have usually a higher protein content and a higher specific gravity, generally above 1.018, but the content in non-protein constituents of exudates, as well as of transudates, resembles closely that of the blood plasma.

For the sake of comparison with pathological tissue fluids and lymph, together with the consideration of the chemistry of edema fluids, the chemistry of normal lymph must be briefly reviewed. For this purpose we are concerned chiefly with analysis of lymph obtained from the peripheral lymph vessels, or from the thoracic duct during fasting, since the composition of lymph from the thoracic duct is considerably modified during absorption from the small intestine. Lymph from the peripheral lymph vessels, or from the thoracic duct during fasting, is usually water clear, of a yellowish green or grayish yellow color. It flows easily, and has a specific gravity of 1.016 to 1.023. It coagulates rapidly on standing. It is poor in total solids, containing from 3.8 to 5.7 per cent, the variation depending chiefly on the protein content.

The *protein constituents* of edema and of normal lymph include all of the fractions found in the blood plasma, although not necessarily in the same relative proportions. Analysis of cutaneous and other effusions have been published by Epstein(*a*)(1914), Tables I and II. These may be compared with analyses of normal lymph, of which the protein content averages about 3.4 per cent, the average ratio of globulin to albumin being about 2.4 to 4. Epstein(*b*) calls particular attention to the low protein content and the high proportion of globulin in the serum and serous effusions of chronic parenchymatous nephritis.

TABLE I

CHEMICAL COMPOSITION OF CUTANEOUS EFFUSIONS

(*Epstein*)

Case No.	Total Protein	Incoagulable Nitrogen	Total Globulin	Eu-Globulin	Pseudo-Globulin	Albumin	Chlorid	Total Solids	Ash	Per cent of Globulin in Protein
	Grams per 100 c.c.									
	NEPHRITIS									
4	0.098	0.004	0.080	0.048	0.032	0.018	0.406	1.230	0.98	81.0
44	0.171	0.162	0.104	0.091	0.095	.....	0.397	....	...	56.1
29	0.145	0.063	0.079	0.024	0.055	0.066	0.433	1.357	0.87	54.0
	CARDIONEPHRITIS									
14	0.462	0.035	0.155	0.032	0.123	0.307	0.412	1.515	0.950	28.5
70	0.119	0.035	0.043	0.018	0.025	0.076	0.420	....	....	30.0
201	0.100	0.053	0.018	....	....	0.082	0.400	....	....	18.0

The *non-protein constituents,* such as urea, uric acid, and creatinin, occur in transudates and exudates in approximately the same concentration as in the blood. Creatin occurs only in small amounts in transudates, but is present in exudates in the same amounts as in blood. Fat and cholesterol occur in small amounts in transudates, but in large amounts in exudates. Analyses of the non-protein constituents of three fluids are reported by Denis and Minot(*a*) (Table III), and are compared with the composition of the blood, withdrawn at the same time. Denis and Minot have shown that the content of edematous fluids in urea, uric acid, and cholesterol may be easily influenced by diet. Javal and Adler have also

TABLE II

AVERAGE COMPOSITION OF EFFUSION FLUIDS

(*Epstein*)

Diagnosis	Serous Fluids			
	Total Protein	Globulin	Albumin	Globulin
	Grams per 100 c.c.			Per Cent
Cardiac Conditions	3.352	1.199	1.788	43.0
Hepatic Cirrhosis	3.174	1.318	1.856	41.0
Chronic Parenchymatous Nephritis	0.285	0.285	0	100.0
	Subcutaneous Fluids			
Chronic Parenchymatous Nephritis	0.098	0.080	0.018	81.0

TABLE III

NON-PROTEIN CONSTITUENTS OF EDEMA FLUIDS

(*Denis and Minot*)

	Ascitic Fluid Cirrhosis of Liver Sp. Gr. 1.012		Chest Fluid Heart Failure Sp. Gr. 1.018		Chest Fluid Tuberculosis Sp. Gr. 1.022	
	Mg. per 100 c.c.		Mg. per 100 c.c.		Mg. per 100 c.c.	
	Fluid	Blood	Fluid	Blood	Fluid	Blood
Total Solids	2315.0	....	4400.0	...	5952.0	...
Total Protein	1693.0	....	3324.0	...	4548.0	...
Non-Protein N	56.0	52.0	23.0	26.0	22.0	25.0
Urea Nitrogen	28.0	26.0	11.0	13.0	11.0	12.0
Uric Acid	3.8	3.6	2.4	2.6	2.5	2.0
Creatinin	1.0	1.3	1.1	...	0.8	...
Creatin + Creatinin	3.3	9.2	4.6	8.0	6.8	8.9
Sugar	155.0	90.0	117.0	...	95.0	90.0
Total Fatty Acids	79.0	866.0	226.0	...	650.0	910.0
Total Cholesterol	25.0	276.0	89.0	...	108.0	250.0
Sodium Chlorid	800.0	....	700.0	...	680.0	....

shown that urea diffuses uniformly through the fluids of the body. An active interchange of these substances between the blood and the edematous fluids seems to be a constant phenomenon, as it is between the blood and normal lymph, since the non-protein nitrogenous constituents are present in the lymph in about the same concentration as in the blood plasma.

Sugar is found in edema fluids, in amounts equal to those in the blood (Hegler and Schumm). In certain cases, however, particularly in ascitic fluids, it may be found in amounts in excess of the blood content. Sittig has found both glucose and levulose in a number of cases. Sugar is also found in normal lymph in about the same concentration as in the blood plasma.

The *total molecular concentration,* as measured by the freezing point method, and the *concentration of electrolysis,* as evidenced by the electrical conductivity, have been studied by numerous authors. In general, the depression of the freezing point approximates very closely that of the blood serum of the same individual, as will be seen from the results obtained by Javal (Table IV). The data obtained by determining the freezing point indicate an approximate osmotic equilibrium between the blood and the edema fluid. The depression of the freezing point, both for blood serum and for edema fluid, is usually within normal limits, except in cases in which the content of non-protein substances, such as urea, is increased.

The *chlorid content,* the *conductivity,* and the *freezing point* have been studied by Baylac and by Boden (Tables V and VI). The chlorid content varies considerably in its relation to that of the blood serum, and may be

TABLE IV

FREEZING POINTS AND NON-PROTEIN NITROGEN CONTENT OF VARIOUS FLUIDS

(*Javal*)

Name	Date	Fluid	Point Freezing	Non-Protein N.	Urea N.	Clinical Diagnosis
			°C	Gm. per L.	Gm. per L.	
Er.	June 30, 1906	Serum	—0.69	1.01	0.65	Cardionephritis
		Edema	—0.67	...	0.60	
Ka.	Mar. 23, 1906	Serum	—0.585	...	0.29	Cardionephritis
		Edema	—0.59	...	0.20	
No.	May 3, 1906	Ascitic	—0.545	...	0.29	Heart Failure
		Edema	—0.555	...	0.31	
Mi.	July 18, 1906	Serum	—0.745	2.03	1.54	Acute Nephritis
		Edema	—0.77	2.13	1.72	
		Pleural	—0.74	2.04	1.42	
B.W.	Aug. 30, 1907	Edema	—0.65	...	0.91	Interstitial Nephritis
		Pleural	—0.65	...	0.92	
M.B.	Dec. 16, 1908	Ascitic	—0.54	0.36	0.18	Heart Failure
		Pleural	—0.56	0.43	0.18	
No.	Jan. 21, 1909	Serum	—0.75	2.94	2.51	Uremia
		Pleural	—0.77	2.73	2.34	
M.D.	Jan. 22, 1909	Serum	—0.65	1.66	1.04	Uremia
		Pleural	—0.66	1.68	1.07	
C.D.	Feb. 1, 1909	Serum	—0.57	0.52	0.31	Nephritis
		Pleural	—0.56	0.52	0.31	
		Cer. Spin.	—0.57	0.45	0.29	
	Mar. 4, 1909	Serum	—0.57	0.63	0.42	
		Pleural	—0.56	0.61	0.43	
		Cer. Spin.	—0.59	0.60	0.35	
Na.	Nov. 18, 1909	Pleural	—0.76	2.50	2.31	Uremia
		Cer. Spin.	—0.75	2.49	2.40	

TABLE V

FREEZING POINTS AND CHLORID CONTENT OF EDEMA FLUID, BLOOD SERUM, AND URINE

(*Baylac*)

No.	Diagnosis	Edema Fluid		Blood Serum		Urine	
		Freezing Point °C	NaCl Grams per Liter	Freezing Point °C	NaCl Grams per Liter	Freezing Point °C	NaCl Grams per Liter
I	Edema of Arm	—0.60	6.50	....	...	—0.98	5.00
II	Edema of Arm	—0.59	6.20	....	...	....	...
III	Nephritis	—0.53	5.40	....	...	....	....
IV	Nephritis	—0.56	6.80	—0.58	6.70	—1.40	10.10
V	Acute Nephritis	—0.56	5.50	....	...	....	....
VI	Heart Failure	—0.59	6.50	—0.60	7.10	—1.90	10.80
VII	Heart Failure	—0.54	6.30	....	...	....	....
VIII	Heart Failure	—0.56	5.40	—0.70	7.00	—1.52	9.10

TABLE VI

CHEMICAL CHARACTERISTICS OF TRANSUDATES

(*Boden*)

Fluid	Sp. Gr.	Freezing Point °C	Sp. Cond. Corrected k x 10^4	Total Solids	Ash	Albumin	Fat	NaCl
				Grams per Liter				
1. Ascitic Fluid	1.0168	—0.56	140.6	46.35	9.04	36.5	0.70	5.50
2. " "	1.0181	—0.57	137.2	49.14	9.39	38.9	2.55	7.26(?)
3. " "	1.0161	....	135.8	38.60	9.88	22.8	0.69	4.86
4. Ovarian Cyst	1.0085	—0.57	144.7	9.61	9.39	2.1	0.01	5.15
5. " "	1.0174	—0.61	146.2	45.87	9.80	35.7	0.32	5.79
6. " "	1.0075	—0.57	145.4	10.62	9.88	2.2	0.01	5.21

either higher or lower than that of the serum, but the total conductivity is not subject to such wide fluctuations, and usually closely approximates that of normal serum. Carlson, Greer, and Luckhardt studied the composition of normal lymph, obtained from the neck lymphatics of the horse, in its relation to the composition of the blood serum of the same animal. They found in each of thirteen experiments a higher concentration of total salts and of sodium chlorid in the lymph, but found the average depression of the freezing point of the lymph to be identical with that of the serum. In dogs, according to Luckhardt, the conductivity of the cervical and thoracic lymph is uniformly higher than that of the serum.

The reaction of edema fluids is stated by Sörensen and by Bottazzi to be approximately that of blood. Fränckel has determined the hydrogen ion concentration in five ascitic fluids, and has found the values for pH $\left(\log \frac{1}{[H^+]}\right)$ to be 7.41, 7.30, 7.98, 7.47, 7.26, the commonly accepted values for normal blood serum lying between 7.35 and 7.40. Hydrogen ion determinations on edema fluid have also been published by Foà, who reports comparable figures.

The surface tension of transudates is higher than that of exudates, the difference being ascribed by Trevisan to the difference in globulin content.

All of the enzymes of the plasma may appear in edematous fluids, especially in exudates. Among those which have been identified are lipases, oxidases, proteolytic ferments, and peptid-splitting enzymes.

Immune bodies, including cytotoxins, hemolysins, bacteriolysins, and agglutinins are found in both transudates and exudates, though usually in greater amounts in the latter. Delrez has studied the biological characteristics of transudates and exudates, and has found no hard and fast distinctions between the two. He states that all of the colloids peculiar to the plasma are found in exudates and transudates, in approximately

proportionate amounts. He has found complement in a newly formed hydrocele in quantities equal to those found in inflammatory exudates. Antibodies pass freely into both varieties of fluid, and Delrez has found, in cases of syphilis, a positive Wassermann reaction, with the same titer in edema fluid as in the blood.

The *toxicity* of edema fluids has been studied by Boy-Teissier. Transudates have been found to be without toxic action on animals.

PART III

The Pathological Physiology of Edema

From the standpoint of pathological physiology there may be considered: (1) the possibility of alteration in the mechanism of the entrance of lymph into the lymphatics and its flow through them; (2) changes in the metabolism of the tissue cells, which might influence the movement of fluid; (3) changes in the permeability of the capillaries, especially in conditions associated with edema; (4) circulatory changes, and (5) changes in renal excretory function. It is the purpose of this section to present the facts ascertained by study, leaving an analysis of their significance to a later section (Part IV).

Definition of Terms.—It is necessary to define accurately the use of certain terms, since there exists considerable confusion in the literature with regard to them. The following definitions are adopted for use in the discussions to follow. The term *lymph* is used only to describe the contents of the lymph vessels, the term *tissue fluids* being used as a general term to designate the fluids outside of the capillaries but not in the lymph vessels. They are divided into *intercellular fluids* and *intracellular fluids. Lymph production* is a general term for the process involved in the production of lymph, including *fluid exchange,* that is to say, exchange of fluid, with its dissolved and suspended substances, in both directions between the capillaries and tissues. *Edema* indicates a pathological increase in intercellular fluids.

Disturbances in the Flow of Lymph.—In man localized edema frequently follows injury or blocking of the lymph channels. A common example is elephantiasis, in which there is blocking of the lymphatics of an extremity by parasites, such as Filaria. The rôle of alterations in the lymph flow in the production of generalized edema, however, is not known. Cohnheim, and also Klemensiewicz, believed that any increase in the transudation of fluid from the capillaries is followed by an increase in the lymph flow, but that edema occurs in spite of this, because the lymphatics are unable to care for more than a certain amount of fluid.

If this assumption were true, one should expect to find the superficial

lymph vessels dilated at autopsy in cases of generalized edema. Volhard found, however, that in most cases this was not true, and he noted a marked overflowing of the abdominal lymphatics in only two cases, in both of which death occurred suddenly during diuresis. He concluded that the lymph vessels have a great deal to do with the disappearance of edema, especially during diuresis, but that they play little part during the time that edema persists.

Cell Metabolism and Edema.—Various authors, Landerer, Lazarus-Barlow, Loeb, Ziegler, Fischer, and Quincke have attributed edema to disturbances of the mechanism by which the tissue cells withdraw fluid from the blood and withhold it from the circulation. Although their conceptions of the disturbance differ their conclusions rest upon the assumption of a disturbance in cell metabolism.

Cell Respiration and Edema.—Following the work of Araki(*c*), in which he showed that diminished oxygen supply to the tissues resulted in incomplete oxidation of the products of metabolism, and the consequent formation of lactic acid, Loeb(*c*) showed that interfering with the oxygen supply might result in the swelling of the tissues and attributed this to an increase in osmotic pressure, the result of acid formation.

On the basis of experiments on the muscles of the frog's leg, similar to those performed by Loeb, Fischer also came to the conclusion that edema is due to increased acid formation. He attributed the edema to swelling of the colloids, since increased acidity is known to increase the affinity of colloids for water. Although there is some evidence of disturbances of cell respiration in conditions associated with edema, particularly on account of the formation of lactic acid in passive congestion, such acid formation has not been shown to increase either the osmotic pressure of the tissues, as Loeb thought, or the affinity of the colloids for water, according to Fischer.

Protein Metabolism and Edema.—Edema caused by *protein poisoning,* as the result of ingestion or administration of foreign proteins, is a part of an anaphylactic reaction. The pathological physiology of edema of this form, usually manifested as urticaria or angioneurotic edema, is not understood.

Edema due to *protein deficiency* has been most striking in the cases of war-edema or famine-edema which have been found frequently in the last few years in the middle European countries (see Schnittenhelm and Schlecht). It occurs apparently as a result of long-continued dietary deficiency (Maver), and is probably due to lack of sufficient protein in the diet (Kohman). There is no evidence of renal excretory insufficiency, and patients usually recover rapidly when put to rest in bed and given a salt poor diet.

Inorganic Metabolism and Edema.—The occurrence, persistence, or disappearance of edema may depend either on the fluid or salt intake, or

TABLE VII

BLOOD SERUM ANALYSES IN SODIUM BICARBONATE EDEMA

(*Falta and Quittner*)

Diagnosis	Diet	Before $NaHCO_3$		After $NaHCO_3$		
		NaCl	Freezing Point	NaCl	Freezing Point	
		Per Cent	°C	Per Cent	°C	
Normal	Mixed	0.64	—0.56	1.00	—0.59	No edema
Hypertension	Salt-poor	0.61	—0.59	0.98	—0.60	No edema
Diabetes	Salt-poor	0.66	—0.58	0.80	—0.60	No edema
Diabetes	Salt-rich	0.64	—0.59	0.61	—0.60	Edema
War-edema	Salt-rich	...	...	0.61	—0.59	Edema

on both. The effect of *salt feeding* and *salt restriction* on edema was observed by Widal, and independently by Strauss(*g*). Their observations have since been amply confirmed. The favorable effect of limitation of fluid intake, or the unfavorable effect of giving large amounts of fluid was emphasized by Bartels(*c*). The degree to which edema is influenced by fluid and salts varies widely in different cases.

That the effect of fluid and salts on edema is due to their rôle in the metabolism of the tissue cells should not be regarded as established. The results of clinical observations have, in fact, usually been interpreted as evidence to the fact that the renal excretory function, with respect to these substances, is impaired.

The administration of large doses of *sodium bicarbonate,* especially in individuals who have already some disturbance in metabolism, is frequently followed by generalized edema. This has frequently been observed in diabetes, but has also been seen in individuals suffering from inanition, or from the results of dietary deficiency, such as that responsible for war-edema. Falta and Quittner have studied this condition and have found that in young healthy adults the same régime which almost without exception causes edema in diabetics, causes no edema. In diabetics, with or without acidosis, administration of large amounts of sodium bicarbonate, together with a diet rich in salt, produced edema in the majority of cases. In diabetes this edema could be prevented or caused to disappear by the withdrawal of salt from the diet, and could usually be made to disappear by the administration of such diuretics as diuretin. It was accompanied by the retention of large amounts of salt, which later left the body rapidly during the disappearance of edema. In these cases the chlorid content of the serum was found to be diminished rather than increased (Tables VII and VIII). The excretion of uric acid and urea was not influenced by the course of the edema. Similar findings were obtained in cases of war-edema.

TABLE VIII

ANALYSES OF BLOOD AND EDEMA FLUID IN WAR-EDEMA

(*Falta and Quittner*)

War-Edema, after administration of $NaHCO_3$, at height of edema.

Blood
Red cells, 3,120,000 per c.mm.
Hemoglobin, 74%
Non-protein nitrogen, 17 mg. per 100 c.c.
Uric acid, 1.74 mg. per 100 c.c.
Creatinin, 1.04 mg. per 100 c.c.
Sugar, 0.0614%
Freezing point, —0.58° C.

Blood serum
Total ash, 0.714%
NaCl, 0.61%

Edema fluid, obtained by subcutaneous puncture
Protein nitrogen, 16 mg. per 100 c.c.
Non-protein nitrogen, 10 mg. per 100 c.c.
Uric acid, negative
Freezing point, —0.60° C.
NaCl, 0.92%, 1.05%, 0.94% (3 samples)

War-Edema, without $NaHCO_3$

Edema fluid, obtained by subcutaneous puncture
Protein nitrogen, 14 mg. per 100 c.c.
Non-protein nitrogen, 12 mg. per 100 c.c.
Uric acid, trace
Sugar, 0.0654%
Freezing point, —0.57° C.
Total ash, 0.814%
NaCl, 0.80%

The Role of the Thyroid in Edema.—Eppinger(*d*), impressed by the diuretic action and apparent curative properties of thyroid extract, at least in certain forms of edema, undertook a study of the mode of action of thyroid extract in relation to lymph production and to edema. He found in normal individuals, and by animal experimentation, that giving thyroid extract appears to have the specific effect of diminishing the ability of the cells to hold water and salt, so that these substances return to the blood and are excreted at an increased rate. He found no direct effect of thyroid extract on the function of the kidneys. On the other hand, extirpation of the thyroid gland resulted in increased storing of water and salts in the tissues, and consequent slowing of the rate of excretion.

In the therapeutic use of thyroid extract striking results were obtained in cases of edema in chronic parenchymatous nephritis, in chronic diffuse nephritis with degenerative changes, and in cases of myocardial insufficiency in which there was disproportion between the severity of edema and other objective findings. No effect was noted in ascites in cirrhosis of the liver. Certain cases of edema, clinically similar to those in which good results were obtained failed, without apparent reason, to respond to this form of therapy.

Eppinger, while convinced that the beneficial results of thyroid extract are due to its effect on cell metabolism, does not conclude that these cases represent an atypical form of myxedema, but believes that the therapeutic results suggest an association between hypothyroidism and edema. He regards functional hypothyroidism, due to passive congestion, as a possible explanation in a certain proportion of the cases. The histological investigation of the thyroid gland to ascertain whether associated anatomical changes take place, was without result.

Capillary Permeability and Edema.—The normal permeability of the capillary walls for certain substances is known to be very great, in that these substances pass through freely and rapidly in either direction. Magnus showed that by injecting hypotonic, hypertonic, and isotonic salt solutions intravenously, salts, water, and albumin could be made to pass in either direction through the capillary walls.

Klicowicz also showed that such salt as sodium sulphate or sodium phosphate, although foreign to the usual metabolic processes, would pass through the capillary walls as readily as sodium chlorid.

Modrakoski and Halter, working in Falta's clinic (referred to by Falta and Quittner), have shown that by injecting small doses of the infundibular portion of the hypophysis they can produce a marked diminution of the protein concentration of the venous blood, together with an increase in the chlorid content, the total molecular concentration remaining unchanged. These changes result apparently from the transfer of tissue fluids to the blood. A normal status returned within a few hours. On the other hand, adrenalin increased the concentration of red blood cells and hemoglobin, without change in the salt concentration. In both cases the capillary walls must be regarded as quite permeable for water and for certain substances which pass in either direction as conditions demand.

It is also known that after an intravenous injection of large amounts of sugar, osmotic equilibrium is regained within half a minute after the termination of the injection (Starling(*a*)), by the transfer of sugar to the tissues. In a similar manner Van Slyke and Meyer(*b*) have shown that after injection amino acids disappear from the blood very rapidly and may be recovered in the tissues.

It can be demonstrated under the microscope that under local chemical, mechanical, or thermal influences, the passage of certain constituents of the blood through the capillary walls is increased. This transfer is seen in local edema, due to inflammation or to the toxic action of iodin or of quinin. In such cases, on the other hand, the rate of passage of tissue fluids into the capillaries seems to be diminished.

Other evidence of increased permeability of the capillaries is based on the more rapid disappearance of substances from the blood, or on the occurrence of edema, after the administration of toxic substances. Magnus

found, for instance, that artificially induced hydremic plethora would cause edema after the administration of arsenic, cantharides, uranium, chloral hydrate, or ether, or after extirpation of the kidneys. This evidence, while demonstrating increased rate of transfer through the capillary walls, does not necessarily indicate altered permeability, since the possibility of a direct influence on the cell metabolism has not been excluded.

Those investigators who have been impressed by the importance of increased permeability of the capillaries as a factor in the occurrence of edema are not unanimous in their opinions as to the cause. Certain writers have assumed that there is retention of toxic substances by the kidneys, others that there is formation of toxic substances in diseased kidneys. Others believe that toxic substances responsible for nephritis itself exert also a damaging effect on the capillary endothelium. In heart failure it has been assumed that either excess of carbon dioxid or reduced oxygen tension is injurious to the endothelial cells, resulting in an increase in their permeability.

Circulatory Changes and Edema.—Complete obstruction of the chief vein from an extremity or a viscus, under experimental conditions, is usually not sufficient to cause local edema, unless there is also obstruction to the lymph return. In man, however, venous obstruction causes edema in a lower extremity. Obstruction to the portal circulation, in cirrhosis of the liver, is generally assumed to be the cause of ascites. The most important factors involved in circulatory disturbances are the rate and volume of blood flow, the arterial, capillary and venous blood pressure, the volume of circulating blood, and the physico-chemical constitution of the blood.

Rate and Volume of Blood Flow.—In heart failure, alterations in the peripheral circulation of blood are well recognized (Lundsgaard(*b*)(*d*)). These include changes in the rate and volume of blood flow, and in the capillary and venous pressure. The degree of edema usually parallels the degree of circulatory disturbance. Alterations in the blood flow are also seen in the edema of chronic interstitial nephritis, when the edema is due to associated heart failure. That such edema is due simply to the mechanical influence of the altered pressure, or rate and volume of blood flow, is not clear, for these changes are associated with certain changes in the chemical constitution of the blood, due mainly to insufficient aëration in the lungs.

Blood and Plasma Volume in Edema.—Various theories of edema depend upon the assumption that there is alteration of blood or plasma volume. Attention has already been called to the theories of Stewart and of Bartels, who assumed that retention of fluid by the kidneys causes hydremic plethora, which in turn leads to edema. On the other hand, those writers who have concluded that the cause of edema lies in disturb-

TABLE IX

TOTAL BLOOD AND PLASMA VOLUME AS RELATED TO BODY WEIGHT

(*Bock*)

Diagnosis	Date	Body Weight	Edema	Total Plasma Volume		Total Blood Volume		R.B.C.
		kilos.		c.c.	% of B.W.	c.c.	% of B.W.	millions
Av. 5 normals		67.0	0	3414	5.1	5467	8.2	4.8
Chronic Nephritis	Jan. 9	54.5	+++	2200	4.0	2587	4.7	2.0
	" 24	46.0	++	1900	4.1	2317	5.0	2.5
	Feb. 3	41.0	0	1690	4.1	1965	4.8	2.4
Diabetes	Jan. 23	50.0	0	2136	4.2	3337	6.6	6.0
	" 27	54.0	±	2376	4.4	3592	6.6	5.0
Cardiac Failure	Apr. 16	72.2	+++	3333	4.6	5847	8.1	5.0
	" 20	61.3	±	3170	5.1	5582	9.1	5.0

ances in the tissues have been impressed by the increased molecular concentration of the blood and the polycythemia in chronic heart failure, and by the apparent dilution of the blood during the period of diuresis accompanying the disappearance of edema, and have been ready to assume that the volume of the blood might be diminished during the persistence of edema. Krehl(*d*) has considered the possibility of an increase in the volume of the blood as a part of generalized edema, that is to say, an "edema of the blood," and states that there is no reason why an increase in the volume of the blood should not take place. On account of divergence of opinion as to the part played by the total blood and plasma volume in the occurrence of the edema, it is of importance to consider the evidence as to their actual state.

Bock(*b*) has recently studied the plasma volume and the total blood volume in various conditions, using the vital red method of Keith, Rowntree, and Geraghty. He finds significant variations in the total blood volume in certain pathological conditions associated with edema, but finds that the ratio of the volume of blood plasma to body weight is practically unchanged (Table IX). He also finds that in edema the relation of the volume of blood plasma to the body weight remains undisturbed during changes of the water content of the body.

It will be seen, from Bock's data, that in none of his cases is there an increase in the relation of the total blood volume to the body weight. In the case of chronic nephritis with anemia there is a diminution in the ratio of the total blood volume to the body weight, corresponding to the diminution in volume of red blood cells, since in this case, as in the others, the ratio of the plasma volume to body weight remains unchanged. Bock has been particularly impressed with this relative constancy, and regards it as the important result of his work. Attention should be called, however, to the decrease in actual volume of plasma, during the same period

in which edema was disappearing, this decrease amounting in one of the cases to 510 c.c. This would indicate that although the ratio of plasma volume to body weight remained unchanged during the time that edema appeared, there was an increase in actual volume of plasma amounting to about 30 per cent of the original volume. Bock's data would therefore appear to confirm Krehl's suggestion of the possibility of "edema of the blood" as a part of generalized edema. There is no evidence to the effect that the increase in plasma volume precedes or is in any way responsible for the occurrence of general edema.

Composition of the Blood in Heart Failure.—According to present conceptions of the physico-chemical mechanism of the exchange of fluid between the blood and tissues, it is important to inquire into the changes in the composition of the blood in heart failure. It is not possible to conclude, however, that such changes in its physico-chemical constitution as may be demonstrated are responsible for edema, for changes in the tissues themselves may result in changes in the composition of the blood. Changes in the blood are then the results of edema, rather than its causative factors. Such changes as have been demonstrated are summarized in the following paragraphs:

Oxygen Content of Blood in Heart Failure.—The oxygen content of the blood, and particularly the degree of oxygen unsaturation of arterial and venous blood in heart failure, have recently been studied by Lundsgaard(*b*)(*d*) and by Harrop(*c*). Lundsgaard found the oxygen unsaturation of venous blood to be increased beyond the normal limits in all cases, except in instances in which the symptoms of heart failure were rapidly lessening. Harrop found in nine patients seven with an abnormally low oxygen saturation in arterial blood, and four of these regained normal values when the circulatory disturbances were relieved. The lowest value for oxygen saturation found in these cases was 81.4 per cent, as compared with the average value of 95.5 per cent, and a low value of 94.3 per cent in fifteen normal individuals.

Carbon Dioxid Content of Blood in Heart Failure.—Peters found the content of carbon dioxid in the venous blood, when considered in relation to the alveolar carbon dioxid tension, to be increased in heart failure. This condition was attributed by him to impaired aëration of the blood in the lungs. Korányi(*a*)(*b*) and his pupils have correspondingly found an increased depression of the freezing point of the blood in heart failure, which they have attributed to its increased carbon dioxid content, since the freezing point could be restored to normal by driving off carbon dioxid from the blood, and since their findings for the blood of patients with heart failure could be duplicated on the blood of normal individuals, if carbon dioxid were passed through the blood in vitro before the determinations were made.

Reaction of the Blood in Heart Failure.—The dyspnea in heart failure is attributed by Peters and others to an increase in the hydrogen ion concentration of the blood, due to increased carbon dioxid content. Accurate determinations of the actual hydrogen ion concentration of the blood as it exists in the body in heart failure are not available, but such evidence as is at hand indicates that the change in actual hydrogen ion concentration is very slight, though it may be sufficient to account for severe dyspnea.

It now appears (Henderson(*f*), 1920, and McLean, Murray, and Henderson(*b*)) that the regulation of the hydrogen ion concentration of the blood, and of the total electrolyte concentration of the plasma involves a more complex mechanism, including the transfer of various substances between the tissues and the blood plasma, and between the plasma and the red cells, than had previously been believed. In this mechanism hemoglobin (which appears to possess the property of varying its acidity according to the degree of its oxygenation), oxygen, carbon dioxid, bicarbonates, chlorids, and other electrolytes each play a rôle. Not until all the factors in heart failure have been studied can the mechanism of the changes which occur be completely understood.

Sodium Chlorid Content of the Plasma in Heart Failure.—The sodium chlorid content of the plasma in heart failure has been studied by the author (1915). In general, it may be said that the chlorids of the plasma are usually within normal limits or are only slightly increased. A decrease has usually been noted during the diuresis following the administration of digitalis (Table X).

Number and Volume of the Red Cells in Heart Failure.—Korányi and others have noted an increase in the number and volume of the red

Table X

Sodium Chlorid Content of the Plasma in Heart Failure

G.M., male, aged 50. Cardiac hypertrophy, auricular fibrillation, edema.

Date	Weight Kilos.	Urine per 24 hrs.	Blood Urea Grams per Liter	Urea Index (McLean)	Sodium Chlorid			Medication
					Urine Grams per Liter	Grams excreted per 24 hours	Plasma Grams per Liter	
1914								
Oct. 5	71.0	760	0.400	53	13.0	9.8	6.11	.....
" 16	73.0	685	0.500	47	5.1	3.5	5.97	.....
" 23	72.6	1600	0.352	76	10.0	16.0	5.51	Digitalis
" 26	72.0	1680	0.358	82	12.3	20.7	6.11	Digitalis
Nov. 2	72.4	1580	0.396	66	12.1	19.1	6.10	.....

cells in cases of heart failure of long standing. Polycythemia in these cases is assumed to result from diminished oxygen supply to the tissues, analogous to polycythemia produced by living at high altitudes.

Summary.—The changes observed in the blood of patients with heart failure seem to be more concerned with the failure of the lungs completely to oxygenate the blood and to withdraw carbon dioxid from it, than with the failure of the kidneys to carry on their excretory function. The tissues also contribute to the changes in venous blood, partly on account of the increased time during which the blood is in contact with the tissues, and possibly on account of chemical changes in the tissues themselves.

Renal Excretory Function in Its Relation to Edema.—The demonstration by Bright of albuminuria and pathological changes in the kidneys in cases of edema, and the readily observed discrepancy between fluid intake and fluid output in these cases, to which attention was directed by Stewart and by Bartels, have led to the assumption, held for a long time, that edema is due to the failure of the kidneys to excrete water. Later Korányi drew attention to the retention of the products of protein metabolism by the kidneys, and ascribed edema to a consequent increase in the osmotic pressure in the tissues, with resulting retention of water. Widal and, at about the same time, Strauss(*d*), showed that the amount of sodium chlorid in the diet greatly influenced the occurrence and persistence of edema, and assumed that this was due to retention of salt by the kidneys, with consequent increase in osmotic pressure in the tissues.

Pearce(*b*) studied the relative etiological importance of renal injury, vascular injury and hydremic plethora in the production of edema, and concluded that for the production of general edema all three factors are essential, no one of them, and no combination of two, being sufficient.

McClure found that when the ureters of the toad, Anura, were ligated, and the animal placed in water, generalized edema occurred in a short time, and concluded that edema in this case was due to the blocking of urinary excretion. Swingle similarly removed the pronephros of the larval form of Anura and found that when the operation was performed after the pronephros had become functionally active, edema followed the operation and frequently resulted in the bursting of the larva. It is worthy of note, however, that total anuria in man, or under experimental conditions in warm-blooded animals, almost never leads to edema, in spite of profound changes in the chemical and physico-chemical characteristics of the blood and tissue fluids.

In certain diseases, however, notably diffuse nephritis and heart failure, evidences of renal insufficiency are coincident with edema, and since the time of Stewart and of Bartels a causal relation between the two has been regarded as probable. But it should be remembered that a

diminished output of fluid, or of salts, in the urine, during the progress of edema, may be the result of edema rather than its cause. It seems desirable to review the evidence of impaired renal excretory function in various forms of nephritis, particularly in those forms which are associated with edema. Since the changes in the blood are usually assumed to depend on insufficiency of renal excretory function, these changes are considered together with the functional changes in the kidneys.

Chronic Interstitial Nephritis.—A sharp distinction must be made between the edema occurring in various forms of nephritis, in which edema is the natural result of nephritis, and edema which accompanies heart failure, occurring as a complication of nephritis. By far the greater proportion of cases of chronic nephritis and edema are actually cases in which edema is the result of heart failure, rather than a direct result of nephritis.

In chronic interstitial nephritis there is the most pronounced evidence of impaired renal function, especially as regards the excretion of such substances as urea, but also of water and salt. Yet edema occurs in chronic interstitial nephritis only as the result of circulatory failure, and the deficiency of renal excretory function cannot be shown to have any direct bearing on its occurrence. For a discussion of renal function and of the changes in the blood in this condition the reader is referred to the section on nephritis in this volume.

Acute Diffuse Nephritis.—In this condition there is direct evidence of disturbed renal function, as shown by the excretion both of urea and of phenolsulphonephthalein. The high salt content of the blood plasma suggests disturbed excretion of salt. Magnus-Alsleben(*c*), however, has shown that the kidneys in acute nephritis are able, in some cases, to excrete amounts of fluids and of salt far greater than the usual daily output. He gave a patient with acute nephritis a liter of tea to drink and it was practically all retained. The total excretion during the eight hours which followed its administration was only 285 c.c. and sodium chlorid only 0.3 per cent. When the same patient was given an intravenous injection of 800 c.c. of physiological salt solution, the excretion of urine reached 900 c.c. within five hours, and the salt content was 0.6 per cent. Magnus-Alsleben interpreted this result as indicating that in the first instance the fluid was withdrawn from the circulation by the tissues before it had reached the kidneys. He concluded that the kidneys were still able to excrete salt and fluids when they reached the kidneys in sufficiently high concentration.

The blood in acute nephritis is frequently hydremic, in the sense that the protein content is diminished and the specific gravity is lowered, but this condition is not always apparent in the early stages of the disease, when the edema is greatest. The non-protein nitrogen is increased; by

TABLE XI

CHLORID CONTENT OF THE PLASMA IN A CASE OF ACUTE NEPHRITIS

Case No. 2366. T. W., male, age 25 years. Acute nephritis, postpneumonia. Partial recovery. Edema from onset until March 25th, none demonstrable after that time.*

Date 1915	Urine Albumin (Esbach) O. per Liter	Blood Urea O. per Liter	Index of Urea Excretion (McLean)	Sodium Chlorid		
				Urine Gm. per Liter	Gm. per 24 hours	Plasma Gm. per Liter
Feb. 12	5.2	1.123	6.2	1.6	1.76	6.28
" 16	8.2	0.966	6.1	2.9	3.25	6.50
" 19	5.8	0.726	12.0	2.6	3.28	6.33
" 22	5.7	0.848	8.5	2.7	3.50	6.00
" 24	5.7	0.948	6.7	1.8	2.16	5.92
" 28	5.2	0.771	6.4	1.9	3.19	5.97
Mar. 5	4.0	0.821	9.2	2.3	4.60	6.21
" 9	4.8	0.912	8.2	2.3	4.37	6.58
" 13	2.8	0.985	8.3	2.3	4.74	6.60
" 23	1.9	1.328	8.2	2.6	7.00	6.52
" 29	1.5	1.322	7.0	2.9	6.55	7.02
Apr. 4	1.8	1.268	6.8	2.0	4.4	6.60
" 8	1.2	1.260	6.9	1.6	3.2	6.55
" 13	1.0	1.318	6.9	1.15	2.56	6.52
" 19	0.5	0.948	10.1	1.2	2.95	6.47
" 21	0.7	0.886	9.4	1.3	2.7	6.45
" 25	0.5	0.696	14.0	1.0	2.8	6.68
" 29	0.5	0.634	33.0	0.8	3.84	6.56
May 3	0.3	0.541	25.0	1.5	5.4	6.72
" 7	0.2	0.406	56.0	1.6	6.9	6.45
" 11	0.15	0.438	72.0	2.5	6.4	6.49
" 14	0.3	0.382	57.0	3.1	6.82	6.37
" 18	0.25	0.383	92.0	2.3	6.22	6.32
" 21	0.15	0.372	52.0	2.6	6.5	6.33
" 25	0.20	0.386	69.0	2.5	3.6	6.35
" 28	0.70	0.432	41.0	1.0	3.8	6.34
June 1	0.3	0.362	72.0	2.6	4.7	6.20
" 4	0.2	0.373	76.0	4.2	6.3	6.25
" 8	0.2	0.378	70.0	1.5	3.3	6.21
" 10	0.3	0.354	72.0	1.4	5.23	6.04
" 12	trace	0.399	63.0	0.8	1.24	5.99
" 15	0.2	0.395	89.0	2.4	3.94	6.07
" 18	0.3	0.359	66.0	3.6	3.16	6.27
" 22	0.25	0.232	70.0	7.6	5.62	6.36
" 29	0.29	0.317	68.0	4.5	4.05	6.13
July 6	trace	0.313	39.0	2.4	11.05	6.08
" 13	trace	0.371	106.0	1.5	7.08	6.05

* Case observed at the Hospital of the Rockefeller Institute.

far the greatest proportion of the increase being due to increase in urea. The chlorid content of the plasma is often increased (Table XI).

Subacute and Chronic Diffuse Nephritis.—The characteristics of these forms of diffuse nephritis resemble those of acute nephritis, with respect to the occurrence of edema, evidence of impairment of renal excretory function, and changes in the blood.

Chronic Parenchymatous Nephritis.—In this condition the evidence of impairment of renal excretory function is usually relatively unim-

portant, unless there are associated inflammatory changes in the kidneys. In fact, the blood urea is frequently lower than the average normal, and the phenolsulphonephthalein output higher. Volhard has also shown that the ability to concentrate sodium chlorid in the urine is nearly always retained, and that the kidneys are able to excrete large amounts of water within a short time. The latter point has been demonstrated both by rapid administration of large amounts of water and by elevating the edematous extremities.

The changes in the blood in this condition may be striking. According to Volhard, the blood is highly concentrated in the early stages of the disease, when the edema may be greatest. The number of red cells is near the maximum of normal figures, and the viscosity may be increased. As soon, however, as the excretion of water becomes improved, especially in the later stages, there is a marked reduction in the protein content of the blood serum. The specific gravity of the serum may fall as low as 1.015. Both the albumin content and the specific gravity of the urine may be higher than that of the blood.

The protein constituents of the blood serum have been analyzed by Epstein, who has found that there is marked diminution of total protein, but that the loss is entirely in the albumin fraction, whereas the globulin is usually increased. The result is a great increase in the proportion of the total protein represented by globulin (Table XII).

Table XII

Average Composition of Blood Sera

(*Epstein*)

Diagnosis	Grams per 100 c.c.			Per Cent Globulin
	Total Protein	Globulin	Albumin	
Normal	7.400	2.738	4.662	37.0
Cardiac Conditions	6.408	2.240	4.417	33.9
Chronic Interstitial Nephritis	6.704	2.396	4.310	35.7
Chronic Parenchymatous Nephritis	3.928	3.462	0.466	89.2

Epstein also finds the cholesterin content of the blood serum to be markedly increased (Table XIII). This results in a milky or pseudochylous appearance of the serum. Recent analyses of blood serum for cholesterin content by Port(*b*) and by Stepp(*c*) are in every way comparable with those of Epstein. Stepp also publishes analyses of the blood serum of three dogs, after nephrectomy, in which there was marked increase of cholesterin.

The non-protein nitrogen of the blood and the urea nitrogen are often lower than the average normal. In mixed forms of nephritis, or in cases of anuria, the figures may be somewhat higher than normal, but the pure

TABLE XIII

CHOLESTERIN CONTENT OF BLOOD SERA

(*Epstein*)

Diagnosis	Cases	Mg. per 100 c.c.		
		Average	High	Low
Chronic Interstitial Nephritis	24	174	265	100
Uremia	5	133	194	87
Arteriosclerosis	7	163	218	100
Cardiac Conditions	19	157	294	104
Bichlorid Poisoning	2	127	130	125
Chronic Parenchymatous Nephritis	9	559	1230	333

form of chronic parenchymatous nephritis is characterized by low figures for urea and total non-protein nitrogen rather than by an increase.

The chlorid concentration of the serum is generally within normal limits.

Renal Function in Other Conditions Associated with Edema.—In heart failure there is usually evidence of impaired renal function, due to injury of the kidney cells as a result of the circulatory condition, or directly to disturbance resulting from the diminished rate and volume of blood flow through the kidneys. Gerhardt(*c*) has shown, however, at least in some cases of heart failure, that the kidneys are able to excrete large amounts of water or salt, given intravenously instead of by mouth, indicating that ordinarily these substances do not reach the kidneys in sufficient concentrations to effect their elimination.

Ziegler called special attention to the forms of edema in which there are no direct evidences of disease of the kidneys or circulation. In such cases the renal excretory function appears quite normal. This is the case in edema occurring in diabetes, as the result of administration of sodium bicarbonate, in edema due to cachexia or inanition, such as war-edema, and edema occurring in disturbances of nutrition in infants. It is also the case in the hereditary forms of edema described by Milroy, and in various forms of paroxysmal edema (Palmer(*b*)).

Summary.—We may summarize the discussion of the rôle of renal excretory function in the production of edema by saying that there is evidence that impairment of this function may sometimes be an important factor, but that edema occurs frequently without evidence of disturbed renal excretory function, that the conditions in which there is severe disturbance of renal function, such as total anuria and chronic interstitial nephritis, are not accompanied by edema, and that there is no conclusive evidence that disturbance of renal excretory function bears a direct causal relationship to the production of edema.

PART IV

Lymph Production and Edema from the Physico-Chemical Standpoint

The Production of Lymph.—For a complete discussion of the physiology of lymph production the reader is referred to the numerous references on the subject. In the present discussion it will be possible to consider lymph production only from the physico-chemical viewpoint. It may, however, be stated, as originally pointed out by Asher(*a*)(*b*) and since confirmed by many other authors, that a striking fact with relation to the normal production of lymph is that the rate of lymph production and flow depends on tissue activity. It cannot be said that increased lymph production, even under normal circumstances, cannot occur without increased tissue activity, but the evidence seems conclusive that increased tissue activity is always accompanied by an increased rate of formation and flow of lymph.

The theories of lymph production may be divided into two classes: first, those which assume a specific secretory activity on the part of the endothelial cell lining the capillaries; and second, those which attempt to explain the process by applying the principles of physics and of physical chemistry. Knowledge of the physico-chemical factors entering into the process of lymph formation is so lacking in detail that judgment as to the necessity for postulating a specific secretory activity is rendered difficult. In any case, a secretory theory would not dispense with the necessity of considering the physico-chemical factors involved, for only through them, or together with them, can a specific secretory power on the part of the cells be effective.

It is customary to consider the mechanism of lymph formation, flow, and reabsorption separately. These are, however, all associated in the same process, and cannot be independent phenomena. From the point of view of the forces concerned, the subject may be considered from two standpoints: first, that of the fluid which enters the lymphatic circulation from the tissues; and second, that which is returned from the tissues to the capillaries.

The conditions which determine one or the other disposition of lymph resemble the conditions concerned in the flow of water or the flow of electricity. There must first be a source of the substance which is to move, and of energy which is to result in motion. There must also be a gradient or a difference in potential between the points between which movement is to occur. So long as there is movement, stable equilibrium is never actually attained, but there is a correlation reached and maintained between the source of matter and energy, the gradient and the flow, whether

in the movement of water or in an electric current. A similar relation applies to the movement of lymph, whether we consider the movement of water alone or include that of its dissolved substances.

If the tissues are regarded as a heterogeneous system in the physicochemical sense, the liquid phases of the system, each composed of water with dissolved and suspended substances, are represented by the contents of the red blood cells, the blood plasma, the tissue fluids in the intercellular spaces, the intracellular fluids, and the contents of the lymph vessels. These phases are separated from one another by more or less permeable membranes, all of them certainly permeable to water and to certain dissolved substances. The whole system is under a certain pressure, and at the temperature of the body. Both the pressure and temperature, for any locality selected, are approximately constant and uniform. The various phases tend to maintain a correlated state or equilibrium, and any force which tends to disturb this state is met by a shift in equilibrium. Equilibrium, under the conditions of the body, is maintained by a continual shift of volume between the phases, and it is this process which is concerned in fluid exchange and in lymph production.

The mechanism of the entrance of fluid into the lymphatic circulation is not at all clear, especially since the weight of evidence at present is to the effect that the endings of the lymph vessels in the tissues are closed (MacCallum(*b*)), and are therefore not directly continuous with the tissue spaces. Cohnheim believed that lymph is an overflow from the tissue spaces into the lymphatics. In the absence of further evidence, it must be assumed that fluid passes into the lymphatics as a result of the same forces that control its passage through the capillary walls, and that it still remains in equilibrium with the fluid in the tissue spaces until it is carried away from intimate contact with them.

The flow of lymph in the lymph channels is apparently influenced in part by hydrostatic pressure, especially in the larger channels, but the flow of lymph in the smaller lymphatics seems to be due to mechanical pressure from outside, chiefly as the result of muscular activity. Since the lymphatics are supplied with valves at short intervals, the result of such pressure is the movement of fluids in one direction only.

The Nature of Edema.—Under abnormal conditions, the equilibrium which maintains the tissue at a fairly definite volume is disturbed in such a manner as to result in an increased amount of fluid in the tissue spaces or cells themselves—that is to say, in edema. From the standpoint of the theoretical considerations already mentioned a change responsible for such a disturbance may originate in any part of the system just described; that is to say, in the blood, intercellular fluids, the cells, the lymph vessels, or any of the membranes through which exchange of fluid takes place. It is evident that the condition must be maintained by the continuous action of the disturbance which brought it about. Otherwise there

is a shift in the equilibrium back towards normal. The conception of edema as a disturbed equilibrium has been emphasized by Meltzer(*a*) and others.

The occurrence of edema depends then on a derangement of the function which regulates the volume of the tissues. Henderson(*e*)(1916), in a theoretical discussion of volume in the animal organism, points out that there is an external regulatory mechanism for the total volume, which operates chiefly by regulating the volume of urine excreted, and an internal mechanism, which involves the exchange of water between the "infinite assemblage of phases which make up the organism." It is this internal mechanism which we have just discussed. Disturbances in the external mechanism, through their indirect influence on the internal mechanism, are also possible causes of edema. It may be pointed out that just as in regulating volume a disturbance in this function may result in edema, so also may a disturbance, in the opposite direction, result in a loss in volume from the tissues.

Physico-Chemical Factors in Lymph Production and Edema.—The equilibrium involved in the exchange of fluid, with its dissolved and suspended substances, which is responsible for the production of lymph and the regulation of the volume of the tissues, is maintained chiefly by the movement of fluid and dissolved substances *through membranes.* This movement is known as *transpiration,* and it may occur in response to a variety of forces, in each case a difference in potential on the two sides of the membrane being necessary. The forces affecting the movement of dissolved substances are not necessarily those governing the movement of fluids. Actually movement of fluid may occur in one direction and movement of dissolved substances in the other, and equilibrium is then approached through a combination of the two effects. So far as we know, there are no membranes in the body which are permeable to water and impermeable to all dissolved substances, although there are probably different degrees of permeability.

On the basis of the theoretical considerations in a previous paragraph, we may analyze the forces which result in transpiration. In each case, it is clear that any force is active only so long as there is a difference in potential, so far as that particular force is concerned, on the two sides of the membrane, and that when true equilibrium is reached movement no longer occurs under the influence of that force.

The forces which are known to affect the movement of solvents or solutes through membranes are *hydrostatic pressure* (filtration pressure), *diffusion pressure of the solvent, diffusion pressure of the solute,* and *electrostatic pressure.* The influence of each of these forces on the movement of fluid in the animal body is considered separately.

Hydrostatic Pressure.—This is the pressure exerted by a fluid by virtue of its specific gravity or of pressure transmitted to it by compression.

This pressure tends to drive the fluid, together with its dissolved substances, through such membranes as are permeable to it and with which it comes in contact. Hydrostatic pressure was originally considered by Ludwig(*a*) to be the essential factor in lymph formation, and this conception is still strongly supported by numerous authors. According to Ludwig, the hydrostatic pressure in the capillaries is higher than in the tissues, and under the influence of this pressure *filtration* of fluid occurs from the capillaries out into the tissue spaces. The process might be compared with the flow of a solution of sodium chlorid through folded filter paper, as a result of the pressure of the solution in contact with the paper. The rate of filtration, in this case, depends on the pressure of the fluid, its physical properties, and on the permeability of the filter. Starling(*a*)(*b*) considers filtration to be the most important factor in the process of lymph production in regions of the body where the capillary walls are fairly permeable, as in the abdominal regions.

On the basis of filtration, edema may be explained as due to an increased rate of filtration, dependent upon the hydrostatic effect of increased capillary pressure, or upon increased permeability of the capillary walls. Increased permeability is then due either to mechanical injury, increased intracapillary pressure, the toxic effect of accumulated products of tissue metabolism, other poisons, or the injurious effects of lack of nourishment.

According to the majority of the supporters of the filtration theory, there is passage of fluid outward from the arterial end of the capillaries, a current of fluid in the tissue spaces toward the venous end of the capillaries, and a reabsorption of fluid at the venous end. The source of energy for the flow of fluid is the hydrostatic pressure in the arterial end of the capillaries, and the gradient is provided by the diminishing pressure toward the venous end of the capillaries. It is necessary to assume that the pressure in the capillaries falls more rapidly than it does outside of them, and that there is actually a difference in pressure maintained between the contents of the capillaries and the tissue fluids. Hill (1906), however, has pointed out that it is impossible to conceive of a constantly maintained difference in hydrostatic pressure on the two sides of the capillary wall, when fluid is passing freely through such a wall.

There is very little evidence that increased capillary pressure has to do with the production of edema. In fact, the occurrence of edema does not parallel increase in venous pressure, even in heart failure (Volhard), and there is no evidence of increased capillary or venous pressure in chronic parenchymatous nephritis, the condition in which edema is an almost constant phenomenon.

Cohnheim, Magnus, and others have strongly supported the theory of edema as a result of increased permeability of the capillaries, due to increased carbon dioxid, lack of oxygen, poisons from the infection re-

sponsible for kidney disease or nephrotoxins. Volhard accepts this explanation as the primary cause of edema, but he finds it necessary to add to it the conception of disturbance of the reabsorption of fluids from the tissues by the capillaries.

On the basis of the theoretical considerations outlined above, we may accept an altered permeability of the capillary walls as a cause of edema, if the permeability becomes altered to such an extent that there is actually leakage of molecules of a kind which otherwise would have been held back by the capillary wall. We should then expect to find the protein content of subcutaneous effusions approaching that of the blood serum, or at least exceeding that of the normal tissue fluids. The difficulty of collection has interfered with all efforts to secure normal tissue fluids for comparison. Eppinger(*d*), however, has injected salt solution subcutaneously, with and without gelatin, and has found that three per cent of gelatin in physiological salt solution greatly hinders the appearance of salt in the urine after such injections. On the basis of this indirect evidence he accepts as an important factor in the production of edema a qualitative increase in the permeability of the capillary walls.

If we accept increased permeability of the capillary walls in the quantitative sense, for the passage of substances in one direction, as this explanation has been accepted by some recent writers (Volhard), we must assume a specific function on the part of these cells, similar to the function of cells having to do with secretion, since permeability in one direction only is not recognized in non-living membranes. The situation is analogous to that in the lungs, as was disclosed in the recent discussion on the oxygenation of blood. Certain investigators believed that alveolar epithelium actually secretes oxygen into the blood, while others believed that the whole phenomenon is readily explainable on simple physico-chemical grounds.

Certain other phases of the effect of hydrostatic pressure seem to be of importance in the occurrence of edema, especially as they relate to the flow of lymph through the lymph channels. In the edema of heart failure the influence of gravity seems to be of particular importance. This influence is readily observed on inspection of the patient. The localization of edema depends on a combination of all the other forces concerned and the effect of gravity. Edema occurs first in regions where the effect of gravity tends to hinder venous and lymphatic return, and occurs late or not at all in regions where the effect of gravity tends to facilitate this return. From these considerations it follows that hydrostatic pressure, and particularly the influence of gravity, is a factor in the equilibrium at all times, and may prove to be the factor which determines edema.

Diffusion Pressure.—Diffusion pressure is the force which results in the movement of molecules or ions in a solution, from regions of greater to regions of lesser concentrations. In a solution we may differen-

tiate the *diffusion pressure* of the solute, and the *diffusion pressure* of the solvent, which is related to what is known as *osmotic pressure.*

Diffusion in the sense of movement of molecules of solute to regions of lesser concentration, was considered by Ludwig to play a part in lymph formation, and is generally recognized as an important factor in the process. It certainly plays a large part, if not the major part, in the transfer of oxygen from the blood to the tissues, and in the return of carbon dioxid, in the form of carbonic acid, to the blood. It may be considered as the major force concerned in the distribution of urea and other non-protein nitrogenous substances, and it is also concerned in the movement of electrolytes and their ions. Diffusion influences both the movement of molecules through membranes and in fluids where membranes are not concerned. Since diffusion pressure of solutes is not in itself responsible for the movement of solvents it probably plays only a secondary or indirect part in the production of edema.

Osmosis, or the passage of a solvent through a membrane permeable to it, but not to the dissolved substance, occurs as the result of the diffusion pressure of the solvent, or the tendency of molecules of the solvent to move to regions in which these molecules are in lesser concentration, or, in other words, to regions in which the molecules of the solute are in greater concentration. The property of a fluid, by virtue of which it can attract molecules of water through a membrane, is generally known as *osmotic pressure.* Osmotic pressure may be defined as the pressure which it is necessary to apply to a fluid to prevent molecules of water from diffusing into it through a semipermeable membrane. Osmotic pressure is, therefore, not a force in itself, but is rather a negative pressure, insofar as it can be considered as a pressure at all.

As has already been pointed out, there are no strictly semipermeable membranes in the body. When a difference in osmotic pressure occurs on two sides of such membranes as exist, equilibrium is restored by a combination of osmosis and of diffusion of the solute, which, it will be seen, must act in opposite directions. As osmosis involves the movement of fluid, with a tendency to increase the pressure or volume of the fluid on the side of the membrane on which there was originally the greater concentration, it is also opposed to some extent by the increase in hydrostatic pressure which it produces. Actually, therefore, the movement of fluid, through membranes which are permeable to water and to most dissolved substances, occurs as the result of a balance between osmotic pressure on the one hand and diffusion pressure of the solute on the other hand, and the hydrostatic pressure on the two sides of the membrane. It is this combination of forces which probably has the greatest influence on the regulation of volume in the tissues.

If osmotic pressure has an important part in the continuous movement of fluids, there must be a source of energy resulting in the main-

tenance of a difference in potential, or a gradient in osmotic pressure. A gradient has been attributed by Starling to the blood proteins. He assumes that a difference in osmotic pressure between the blood and tissue fluids, due to the fact that the capillary walls are impermeable to the blood proteins, balances a difference in hydrostatic pressure, so that the direction of the movement of fluid depends on disturbances in this balance. That is to say, under ordinary circumstances the hydrostatic pressure in the capillaries is greater than that outside of the capillaries by an amount corresponding to the difference in osmotic pressure; the osmotic pressure of the blood plasma being also greater than that of the tissue fluids. A continued disturbance of the equilibrium, leading to the flow of fluid from the blood vessels to the tissues, would depend on the outpouring of molecules from the tissue cells, though the nature of the molecules responsible for such disturbances has not yet been determined.

If edema is dependent on osmotic phenomena there must be a source of energy sufficient to disturb the lymph balance so that the volume of the tissues is increased beyond normal limits. Such a source, if it exists, may be looked for in the metabolism of the cell. This source, according to Loeb, is the altered metabolism due to diminution of the oxygen supply. Araki had already shown that a diminution in the oxygen supply resulted in the formation of lactic acid by the tissues. Loeb showed that this condition was accompanied by swelling, which he attributed to increased osmotic pressure.

There is known to be production of lactic acid in the tissues in at least some cases of heart failure. Peabody, Meyer, and DuBois, and Peabody, Wentworth, and Barker have shown, however, that there is a normal or increased consumption of oxygen in severe cases of heart failure, and that there is a normal respiratory quotient, indicating that there is no profound change in intermediary metabolism. In addition, the studies of Lundsgaard show that though there is increase in the degree of oxygen unsaturation of the venous blood in heart failure, edema may persist in spite of the fact that the venous blood contains approximately one-half of the oxygen content of the arterial blood; that is to say, even when the degree of oxygen unsaturation in the venous blood is within normal limits. It may not be correct, therefore, to speak of lack of available oxygen in heart disease, though there may be some inability to utilize oxygen properly, and a lowering of the maximal oxygen tension in the tissues. The occurrence of polycythemia in cases of chronic heart failure suggests disturbance in oxygen supply to the tissues.

A further possible source of disturbance to osmotic equilibrium, especially in heart disease, depends on alteration in the heterogeneous acid-base equilibrium, due to the increase of free carbonic acid and bicarbonates in the tissues and in the blood, and to the decrease in oxygen in combination with hemoglobin. Various electrolytes are involved in this

equilibrium, and although their movements in response to disturbance in the acid-base equilibrium are not fully understood, it seems probable that such movements may influence osmotic equilibrium, and hence the regulation of volume. The possible sources of energy for a disturbance of osmotic equilibrium in cases of nephritis are not so easily defined. There is evidence of disturbance in the acid-base equilibrium, particularly in acute nephritis, in the diminished content of bicarbonate in the blood, supposedly due to the retention of acids by the kidneys, but so far this disturbance has not been definitely related to the occurrence of edema.

Epstein, on the basis of his chemical analyses of the serum proteins in chronic parenchymatous nephritis, and on Starling's theory in regard to the balance between difference of osmotic pressure and hydrostatic pressure between the capillaries and tissue fluids, ascribes the occurrence of edema to the loss of protein from the blood plasma, and a corresponding diminution in the difference between the osmotic pressure of plasma and tissue fluids, resulting in a relative increase in the osmotic pressure of the tissue fluids. The evidence in favor of this theory consists entirely of favorable results in a series of patients treated with high protein diet, in an effort to restore to the body its lost protein. In such cases the composition of the blood plasma was brought back towards normal, and edema which persisted during other methods of treatment, improved or disappeared. MacLean and DeWesselow, while confirming the favorable effects of high protein diet in edema due to chronic parenchymatous nephritis, have shown that a favorable influence may be observed without any change in the protein content of the plasma. Their results seem, therefore, to throw doubt on Epstein's theoretical interpretation of his results.

Hydrophilic Action of Colloids.—Changes in the content of free water of the tissue fluids, and hence readjustment of volume through the forces just discussed, particularly hydrostatic pressure and diffusion pressure of the solvent, are believed by Fischer to be responsible for the occurrence of edema. Fischer's explanation of the process, though based originally on the findings of Araki(*c*) and of Loeb, includes a consideration of factors hitherto deemed unimportant in the process.

Fischer attributes edematous swelling in the tissues to an increased inhibition of water by colloid substances, due to increased acid formation. That colloid substances do swell in acid solutions is well known. Fischer, however, has brought forward no quantitative evidence to show that this swelling of colloids occurs, under conditions in the body, to an extent sufficient to account for the phenomenon of edema. Henderson, Palmer, and Newburgh have moreover shown that the extremes of acidity necessary to cause a significant swelling of colloids, outside of the body, are far beyond the range of acidity found in the body, or compatible with life. Crozier has shown also, by the aid of indicators, that the range of

intracellular acidity, compatible with the life of the cell, is far too limited to induce colloids to swell.

In view of the observations of Loeb(*b*)(1918) on the influence of the hydrogen ion concentration on the various properties of colloids, including swelling, it may be regarded as proved that the increased affinity of colloids for water depends not on any increase in acid content, as such, but on the actual hydrogen ion concentration of the medium in which the colloids are suspended. There is no evidence to show that edema is accompanied by significant variations from the normal of hydrogen ion concentration of normal blood plasma, and such analyses as are available (Fränkel, Foà, Bottazzi, Sörensen) indicate a very close approximation of the hydrogen ion concentration of edema fluids to that of blood plasma.

The theory of Eppinger that, under the influence of certain toxic substances in the blood in nephritis, the permeability of the capillary walls is qualitatively changed to permit large colloid molecules to pass out from the blood, has this point in common with Fischer, that both have postulated a leakage of albumin from the capillaries into the tissues. While Fischer bases the retention of water on the swelling of these colloids, due to an increased production of acid, Eppinger suggests simply the retention of fluid in the intercellular spaces by the increased osmotic pressure due to the increased content of protein molecules.

Electrostatic Pressure.—The distribution of electrolytes is affected not only by the diffusion pressure of their molecules and ions, but also by the attractive force of oppositely charged ions. Any difference in electrical potential which develops in different parts of a fluid is thus rapidly brought to equilibrium by the migration of ions. Loeb(*c*) (1919) has also shown that under certain conditions the molecules of water may assume an electrical charge, and that the electrification of water, and of the membrane itself, may influence to a considerable degree the movement of fluid through membranes. In view of the differences in potential known to occur in the tissues it seems extremely likely that such differences may have a profound effect on the movement of the fluid. The possibility of this effect and its bearing on physiological processes has not yet been sufficiently considered from the experimental standpoint to permit the statement of an opinion on its influence in the conditions under discussion, but the subject has already received some consideration (Gunzburg).

Influence of Chlorids and Fluids.—The clinical effects of varying intake of chlorids and fluids have been discussed. Although the mechanisms underlying these effects cannot be fully analyzed until the various forces concerned in lymph formation and edema are more clearly understood, certain considerations may be set forth on the basis of the analysis of the forces just discussed.

Cohnheim and Lichtheim found that they could inject physiological salt solution into normal rabbits and dogs, up to 92 per cent of the body

weight, without producing edema. When, however, the capillaries were injured by poisons such ejections caused marked edema, even though the kidneys remained active. Cohnheim concluded that salt and water were retained by the tissues because the blood vessels could no longer hold them, and not on account of insufficiency of the kidneys.

Ambard and Beaujard demonstrated the occurrence of chlorid retention without edema in cases of interstitial nephritis. Brasch has found the sodium chlorid content of the blood as high as 10 grams per liter in cases of anuria, without edema.

Whether the actual cause of retention of sodium chlorid and water in the body depends on insufficiency of the kidneys, or on alterations in the permeability of the capillary walls, or in the cell metabolism, the mechanism of the relation of salt and water intake to edema may be conceived as follows:

The blood, under normal conditions, and even under abnormal circumstances, tends, by some regulating mechanism, to maintain its volume, its concentration of electrolytes, and its osmotic pressure at remarkably constant levels. The forces concerned in this mechanism are those just discussed, but regulation of the mechanism is not understood. Under normal circumstances, any excess of salts or of fluid is rapidly excreted through the kidneys, though these substances may be temporarily stored in the tissues. Under abnormal conditions, such as obtain in heart failure and in nephritis, fluid and salt remain in the tissues to form edema. If, as a result of excretion and diminished intake, the chlorid and water content of the plasma tend to fall below normal, these substances are withdrawn from the tissues, the volume of fluid in the tissues is diminished and edema tends to disappear. The process is analogous to the behavior of these substances in the normal organism, except that the organism as a whole is not able to dispose of the usual excess of fluid and salt ingested. As has been shown, such fluids as remain in the tissues in edema are maintained in appropriate osmotic equilibrium with the blood, so that salt and water have a mutual attraction for each other, and both are necessary for the occurrence and persistence of edema.

PART V

The Treatment of Edema

Only those methods of treatment of edema are discussed which are directed toward the regulation of metabolic processes. For other methods of treatment, especially mechanical methods, treatises on general medicine should be consulted.

Prophylaxis.—As edema is usually a secondary or symptomatic condition, its prophylaxis depends on treatment of the primary condition,

including the early application of such methods as are described below, in order to prevent the accumulation of large amounts of fluid in the subcutaneous tissues and serous cavities. Of especial importance is the early treatment of heart failure, by rest in bed, and proper drug and dietetic therapy, and of infectious diseases by a bland, salt-free diet.

The prevention of the attacks in recurrent forms of edema, such as urticaria and angioneurotic edema, may be possible. An investigation of such patients should be made in order to determine the particular proteins to which the patients are sensitive, so that the patients may be protected from contact with them. In some cases desensitization is possible, by the subcutaneous injection of the appropriate proteins, at first in minute doses, and later in gradually increasing doses. When the attacks are attributed to intestinal disturbances especial attention should be paid to the diet, and to keeping the bowels open. The conditions of the nasal mucosa should be studied; relief is sometimes obtained by the removal of polyps, or the correction of obstructive deformities.

Etiologic Treatment.—Since edema is often improved by treatment designed to relieve the underlying condition it is the first duty of the physician to establish, as early as possible, a diagnosis of the condition responsible for its occurrence. It is especially important to recognize the edema of heart failure, so as to institute appropriate treatment of the cardiac condition. In uncomplicated cases of heart failure, the diagnosis is usually not difficult, but when edema due to heart failure occurs during the course of chronic interstitial nephritis or primary hypertension, it is often mistaken for the edema of nephritis. The results of treatment in cardiac cases are often striking, and the possibility of this etiology should not be overlooked. In case of doubt a patient should be treated as though heart failure were present, and until the therapeutic test has been shown to be negative.

The Edema of Heart Failure.—In cases of heart failure with slight or only moderate edema it is, as a rule, unnecessary to apply therapeutic procedures designed primarily to relieve edema, since in such cases it generally disappears rapidly as the result of measures undertaken to relieve the underlying condition. Rest and digitalis are the important remedies.

In more advanced or severe cases special dietetic measures, particularly limitation of fluid and salt intake, and the administration of diuretics and saline cathartics are often indicated. These measures are discussed below. Special attention should, however, be called to the Karell régime. This régime is indicated in particularly obstinate cases of edema but also is often used as a routine in beginning the treatment of any case in which edema is a prominent symptom.

The Edema of Nephritis.—The edema of glomerulo-nephritis, unless complicated with heart failure, is usually not so marked as to require

special measures for its relief. Diet, with particular reference to the limitation of fluid and salt intake, is of first importance.

Considerable progress has been made within the past few years in the treatment of the edema of chronic parenchymatous nephritis. Rest and limitation of fluid and salt intake are effective in many cases, and should be given a thorough trial. The dietetic treatment advocated by Epstein and the administration of thyroid extract, as advised by Eppinger, have given good results in some cases, and may be instituted if the simple restriction of fluid and salt intake fails to afford relief. Both of these methods are discussed below.

Dietetic Treatment of Edema.—The nature of the diet prescribed is important. In nearly every case milk should form a large part of the diet. It may be supplemented by well-cooked cereals, including, if extreme salt restriction is not required, those already cooked, such as shredded wheat biscuits and corn flakes, by starchy foods, such as toast and unsalted crackers, and unsalted butter. Later soft boiled or poached eggs, chops, fowl, fresh fish, and oysters may be added. A more liberal diet may be permitted as the edema disappears.

Restriction of the fluid and salt intake is of great value in many cases, and often proves the turning point in the control of edema, whether due to heart failure or to nephritis. Unless a patient responds promptly to the simpler methods of treatment the salt intake should at once be reduced to a minimum. Moderate restrictions should be imposed in every case by avoiding the addition of salt in the preparation and serving of food. When, however, a strictly salt-free diet is advisable substitutions must be made for the articles of diet suggested above. The cereals obtained already cooked contain salt, and must be avoided. Potatoes, green vegetables, fruit, and sugar are acceptable constituents of a rigid salt-free diet, when prepared and served without the addition of salt.

The fluid intake should be measured and restricted to the least possible amount without causing actual discomfort to the patient. In the case of patients with only slight edema this procedure is less important, but it should be rigidly adhered to if there is pronounced or particularly obstinate edema. From 800 to 1,500 c.c. in twenty-four hours, including all fluids and not water only, given frequently and in small amounts, usually is sufficient. The common method of procedure is to start with an amount fixed arbitrarily at about 1,200 c.c. This amount can be increased if necessary, or decreased if possible. The absence of salt from the diet makes restriction of fluids result in less discomfort to the patient than when salt is not restricted.

Karell Régime.—The reduction of intake of both fluid and salt may be accomplished very simply, and in edema of heart failure often with remarkable results, by instituting the Karell régime. This consists in giving 200 c.c. of skimmed milk, which is sipped slowly, at eight, twelve,

four, and eight o'clock. No other liquids or solids are given during the day or night for a period of from four to seven days. This régime furnishes 800 c.c. of fluid, 32 O. of protein, 300 calories, and 1.3 O. of sodium chlorid. A régime so deficient in nourishment cannot of course be continued for more than a limited period. Occasionally even more stringent limitation of intake is made for a few days, down to 300 or 400 c.c. of milk per day. It is customary to prescribe a gradual return in the course of the second week to a more permanent diet, which will probably be of restricted but adequate fluid caloric and protein content and of low salt content. With a patient resting in bed the ordeal is usually easily borne, and the results generally justify the procedure. Edema often disappears rapidly, and convalescence is materially shortened.

Epstein's Dietetic Therapy of Nephritis with Edema.—After analyzing the blood serum and edematous fluid from patients with certain forms of nephritis, especially the form known as chronic parenchymatous nephritis (nephrosis) Epstein(*b*) concluded that the cause of edema, in this type of nephritis at least, is "the decreased osmotic pressure of the blood resulting from the diminution of the protein content of the blood-serum, a condition directly due to the steady loss of large quantities of albumin in the urine." According to him, "the altered condition of the blood-serum (and the consequent reduced osmotic pressure) favors the absorption and retention of fluid by the tissues. Hence the great edema and oliguria." The increased lipoid content in the blood in chronic parenchymatous nephritis, according to Epstein, "indicates a state of impaired nutrition, and constitutes an additional disturbing factor in the physico-chemical state of the blood."

On this basis, Epstein states that the indications for treatment are: "first, to increase the protein content of the blood, and thus to restore its osmotic power; second, to remove the excessive lipoids." To effect this result he finds it necessary to give a diet which is rich in proteins and poor in fats. Starchy foods are limited in order to promote the maximum assimilation of proteins and to lessen the production and retention of water.

An example of the diet used by Epstein is as follows:

	per diem
Water	240 c.c.
Milk (skimmed)	360 c.c.
Coffee	180 c.c.
Broth	220 c.c.
Egg white	from 8 eggs
Cracker	1
Matzoths	1
Veal chop	1
Chicken	2 oz.
Vegetables (5% carbohydrates)	250 grams
Vegetables (10% carbohydrates)	100 grams
Orange	1

Epstein reports remarkable results. In his cases, diuresis, with corresponding reduction in the amount of edema, followed very shortly after the diet was inaugurated, and within a few weeks edema was absent, the urinary protein diminished or disappeared, the renal excretory function improved, and the composition of the blood became approximately normal. In one severe case, in which the output of urinary protein had been as high as 41.2 grams in 24 hours, edema disappeared completely and permanently, as well as every trace of the original renal disturbance after six months of treatment. The patient, a young man of 23, was later drafted into the army, and shortly after discharge was accepted by a life insurance company as a desirable policy holder. Favorable results following the Epstein method of treatment have also been reported by Allbutt, MacLean and DeWesselow, Box, and Symes.

Epstein calls attention to the fact that chronic parenchymatous nephritis is often associated with pregnancy, and states that it is necessary to inquire closely into the relation of the process to reproduction, including lactation. He also states that some cases are associated with a certain degree of myxedema, and that although such cases may closely resemble the pure form of parenchymatous nephritis ultimate cure is not attained until the use of thyroid extract is instituted.

Epstein has used the same dietary measures in cases of chronic diffuse nephritis, and in the mixed type of chronic nephrosis with superimposed diffuse nephritis, with favorable results, as far as albuminuria, edema and blood proteins and lipoids are concerned, but without any influence on the course of the nephritis, or upon the impairment of renal excretory function. He concludes that in such cases, in the absence of marked accumulation of nitrogenous waste products in the blood, high protein diet may be used with advantage. If, however, the blood shows extreme retention of these substances, proteins in the diet must be restricted. In such cases the diet should consist largely of carbohydrates until the excess of nitrogenous waste products in the blood is eliminated. Restriction of salt and water is usually also necessary. The amount of fat which should be given with the food must be judged by the lipoid content of the blood.

Drug Therapy.—*Digitalis.*—In cases of heart failure with edema the effect of digitalis is usually marked, and in most cases no other diuretic is needed. Digitalis is also of great benefit in cases of nephritis in which edema occurs as the result of heart failure. In such cases the indications for administration of the drug is the same as in uncomplicated heart failure.

Diuretics.—The diuretics of the theobromin group are often of value in the treatment of edema of heart failure, and may be used to supplement the use of digitalis. Diuretin, or theobromin-sodium-salicylate, in doses of 1.0 gram four times daily may prove effective. If no effect is produced within four to five days further administration is useless.

Theocin in doses of 0.2 to 0.3 gram, or theocin-sodium-acetate 0.3 to 0.5 gram four times daily sometimes produces a remarkable diuresis in patients with general anasarca. It is usually not well borne, however, and it may induce vomiting and purging. In some cases it is without diuretic effect, and in nearly all cases it loses its diuretic effect after two or three days. It is advisable to order its administration for a period of three days and to discontinue its use earlier if its untoward effects become pronounced. If it produces no diuresis within three days further administration is of no benefit.

The administration of diuretics in edema of diffuse nephritis or of chronic parenchymatous nephritis is almost without exception of no benefit, but striking effects are seen in the edema of heart failure complicating chronic interstitial nephritis or hypertension.

Purgatives.—The administration of purgatives is nearly always advisable, but violent purgation with irritant hydragogue cathartics should be avoided. Calomel is of value for its diuretic effect as well as for its purgative action, and should be used in conjunction with a saline cathartic. The most useful cathartic is magnesium sulphate, given in doses of 15 to 30 grams, in saturated solution, and this may be repeated daily, the object being to produce several watery evacuations every twenty-four hours. Other salines, or jalap, elaterin, or podophyllin may be used.

Thyroid Extract.—Eppinger found that the administration of thyroid extract to certain patients with edema resulted in a very great improvement, often in complete disappearance of the edema. His best results were obtained in patients with myocardial disease in which edema was out of proportion to the other signs of cardiac disease, and in chronic parenchymatous nephritis.

Eppinger gives the following indications and contraindications for thyroid therapy in edema:

Indications for Thyroid Therapy.

1. Markedly edematous forms of heart failure due to pure myocardial disease.
2. Certain forms of renal disease.
   a. *Chronic parenchymatous nephritis (nephrosis), with marked edema.*
   b. *Diffuse nephritis, with edema, without evidence of cardiac failure.*

No beneficial effects have been noted in

1. Edema following emphysema of the lungs.
2. Edema following chronic interstitial nephritis.

Contraindications to Thyroid Therapy.

1. Heart failure, with exception of cases of pure myocardial disease.
2. Coronary sclerosis.

Very doubtful, or practically negative results, have been observed in ascites associated with cirrhosis of the liver. Eppinger, however, does not regard this as a definite contraindication for the employment of thyroid therapy.

Eppinger uses thyroid extract only in such cases as have been found not to respond to the usual method of therapy. He finds that the maximal effects are obtained after two or three weeks of administration of 0.9 gram of dried thyroid substance daily. Further administration is without beneficial effect, and can be followed by very unpleasant complications.

The greatest care must be used in the treatment of edema associated with any form of heart failure. At the beginning not more than 0.3 gram daily of the dried thyroid substance should be given. In renal disease larger doses are permissible, but Eppinger prefers to begin with small doses in every case, until the reaction of the patient has been observed. He usually begins with doses of 0.3 gram daily, but advises doses of 0.1 gram daily in cases where extreme caution is advisable. After it has been determined that the general condition of the patient has not been adversely influenced by the therapy, having given special attention to diarrhea and the frequency of the pulse, the dose may be increased to 0.9 gram daily. Larger doses, up to 1.2 grams daily are used rarely. In some cases of renal disease increase of albuminuria and hematuria followed the institution of thyroid therapy.

Intensive thyroid therapy should not be continued for more than three weeks. If the frequency of the pulse, the general effect of stimulation, or of the number of stools are greatly increased within this time, thyroid therapy must either be discontinued or the doses reduced to the minimum. In certain cases, after the maximum beneficial effect has been obtained, it is advisable to continue with small doses over longer periods of time, in order to prevent the recurrence of symptoms. In such cases not over 0.1 to 0.3 gram daily should be given, and especial attention should be given to the signs of intoxication noted above. In some instances it may be necessary to give opium together with the thyroid, to counteract the diarrhea.

Baths.—Hot baths, in order to increase the loss of fluid through the skin, are often beneficial, either in the form of tub baths at 97° F., for about half an hour daily, or an electric light bath, with the patient in the recumbent position. In all cases such therapy should be begun cautiously, in order to avoid unfavorable reactions. In the edema of heart failure it is doubtful whether the results justify the risk involved, but very good results are sometimes obtained in acute nephritis.

Anaphylaxis, Hypersensitiveness, and Protein Intoxication . . . . *Warfield T. Longcope and George M. Mackenzie*

Introduction—The Pathological Physiology of Experimental Anaphylaxis—Etiology—Pathology—Protein Metabolism in Anaphylaxis—Respiratory Metabolism—Heat Regulation—Serum and Cellular Ferments—Non-Specific Alteration of the Degrees of Hypersensitiveness—The Relationship of Experimental Anaphylaxis to Disease in Men—Protein Intoxication.

Anaphylaxis, Hypersensitiveness, and Protein Intoxication

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Introduction.—When the eminent French physiologist, Charles Richet, observed the increased susceptibility of dogs to a second parenteral injection of a glycerin extract from the tentacles of a sea-anemone, he indicated a path for investigation which has since been brilliantly illuminated by many experimenters. Although Richet was the first to appreciate the significance and give the name of Anaphylaxis to this extraordinary phenomenon, the observations of several investigators, beginning with Magendie in 1839, had foreshadowed the discovery of this biological phenomenon.

In the 18 years since Richet's observation, the efforts of scores of workers have added much to our information on this subject, but complete success is far from being attained. The applicability of the essential fact in anaphylaxis to innocuous, as well as toxic proteins, observed first by Flexner in 1894, by Arthus in 1903 and by Theobald Smith in 1904, was amplified by Otto, Rosenau and Anderson, Gay and Southard, Friedmann, Doerr, and Friedberger. With investigations, elimination of the possibility of a cumulative effect in the specificity of the reaction was determined, and it thus became well established that an animal, when injected subcutaneously, intraperitoneally or intravenously with a small amount of foreign protein, was rendered susceptible to a second injection of this same protein made at least 9–14 days after the preliminary dose. While the preliminary or sensitizing dose may be very small, the second or intoxicating dose, in order to produce symptoms, must be considerably larger, but when this is properly gauged and made into the peritoneum or the vein, the animal dies within five minutes to one hour, the symptoms depending somewhat upon the type of animal which is employed for the experiment. This phenomenon is known as active anaphylaxis.

A second condition, known as passive anaphylaxis, described by Gay and Southard, Richet, Otto, Friedmann, and Nicolle, consists in the transfer of specific sensitiveness from a guinea-pig previously injected

with some protein such as horse serum to a normal guinea-pig. When the serum of the sensitized guinea-pig is injected into the normal animal, this animal shows, after a period of 15–18 hours following the inoculation, sensitiveness to an injection of horse serum and, with the appropriate dose, dies in the same manner as the actively sensitized guinea-pig. The condition has been studied particularly in this country by Weil, who, among others, has emphasized the importance of the latent period following the injection of the serum from the sensitized guinea-pig which is necessary before anaphylactic shock can be produced by the subsequent inoculation of horse serum.

There is theoretical importance also to the further observation of Gay and Southard showing that it is possible to sensitize a fresh animal passively not only with the blood of a sensitized animal, but also with the blood of an animal which is in the anti-anaphylactic state.

A third condition which was described first in the pioneer studies of Otto and in those of Rosenau and Anderson, and was made the subject of investigation by Besredka and Steinhardt, is that of anti-anaphylaxis or desensitization, in which, for a short period following the anaphylactic shock, the actively sensitized animal becomes insensible to subsequent injections of horse serum. This period of anti-anaphylaxis is a temporary one, and with its disappearance the animal becomes sensitive to the specific protein and remains so for months or years.

Efforts have been made to determine the quantitative relations between sensitizing dose, length of incubation period, minimal anaphylactic dose and minimal desensitizing dose. The results of Weil, although not in complete agreement with those of other investigators, are as trustworthy as any available observations on these points. Weil found that with a small sensitizing dose, the incubation period is longer and the minimal anaphylactic and minimal desensitizing doses are smaller than when larger amounts are used for the sensitizing dose.

Finally it was shown by Rosenau and Anderson that the repeated injections of horse serum, at intervals of 2–3 days, produce what has been termed a refractory condition towards subsequent injections of the specific protein, so that for a long period of time, animals no longer react to an injection of the protein with anaphylactic symptoms. If, however, injections of serum are stopped the refractory period finally gives way to sensitiveness, and eventually the animal again becomes susceptible. During this refractory period the serum of the guinea-pig is particularly well-adapted to produce the state of passive anaphylaxis in the normal guinea-pig.

The Pathological Physiology of Experimental Anaphylaxis.—The symptoms occurring during anaphylactic shock vary somewhat according to the animal which is used for the experiment. The vast majority of observations have been made upon the guinea-pig, but the anaphylactic

shock has likewise been studied in the rabbit, the cat, the dog, and a few observations have been made upon larger animals.

When an intoxicating dose of the foreign protein to which a guinea-pig has been sensitized is injected intravenously, there occur in about one minute restlessness, bristling of the hair, sneezing and vigorous rubbing of the nose. Within two or three minutes the hind legs become weak. There are violent respiratory efforts accompanied often by convulsive seizures. The animal finally falls on its side, and there are often urination and defecation. The respirations become extremely slow and very shallow, and the animal dies. If the dose is not so large, and is not fatal, the symptoms do not usually progress to complete collapse; the coughing and sneezing and respiratory difficulty are prominent and the pupils are dilated. Gradual recovery ensues, and within a few hours the animal is apparently perfectly well. In the fatal shock the temperature drops, while with smaller or sublethal doses, there may be at first a drop and then a rise, in temperature.

In the rabbit, the respiratory difficulty, which is characteristic of anaphylactic shock in the guinea-pig, may not be observed, but preliminary excitement, later prostration and convulsive seizures and the passage of urine and feces, are very common. The respirations are increased, but the sneezing, coughing and violent respiratory efforts observed in the guinea-pig are absent. Sensitized animals recovering from a sublethal dose of foreign protein may develop a gradually increasing cachexia which may lead to death in a few weeks. It is in the rabbit that Arthus first pointed out that local subcutaneous injections of horse serum, when given every six days in the same site, produce after the fourth and fifth injection, first an edematous infiltration and next the formation of a local gangrene at the point of inoculation. He likewise observed that after four or five injections had been made in the same site, the characteristic local reaction could be brought out by an inoculation of the specific protein in any other part of the body.

In the dog, a re-injection intravenously of the same protein used for sensitization results first in a short stage of excitation lasting scarcely more than a minute. This is followed by swaying and swallowing movements and some retching. The animal stands unsteadily, his head and tail down. Very shortly, the retching is followed by vomiting. The animal staggers and falls to the ground. The breathing is not altered or if changed at all, is slow and deep. There are passage of urine and fecal discharges which are sometimes bloody. With fatal doses the dog dies in collapse.

In the cat, great excitement usually follows intravenous injection of the second dose of protein to which the animal is sensitized. Convulsive seizures and paralysis rapidly ensue when a fatal dose is used. The respirations are very rapid and difficult, and frequently, frothy material exudes from the mouth. The discharge of urine and feces is common.

In man, primary injection of horse serum is followed in a certain proportion of cases by the condition known as serum sickness. The frequency of serum sickness varies to a certain extent with the dose of serum employed, increasing in frequency with the size of the dose until, when 50 c.c. of horse serum are injected intravenously, about 90 per cent of the patients develop serum sickness. The disease usually makes its appearance 7–10 days after the injection of serum and is characterized by the appearance of urticarial, erythematous or scarlatiniform eruptions, by an enlargement of the lymph nodes and, in a certain proportion of cases, fever, edema of the eyelids and of the extremities, and arthralgia. Rarely, there are gastro-intestinal disturbances. In children, as observed by von Pirquet and Pick, there is at first a polymorphonuclear leukocytosis. Later the leukocytes become normal or even decreased in number, and the relative proportion of lymphocytes is increased. Von Pirquet and Schick, who first studied completely this disease, described the above symptoms as occurring in the normal form of serum disease, whereas a second injection, made months or years after the first, might result in the so-called accelerated reaction, in which the above symptoms occurred within 3–6 days after the injection of serum; or a third variety, termed by them the immediate reaction which took place within 24 hours after the injection. Immediate reactions may rarely be fatal and are accompanied by severe and generalized urticaria, engorgement of the face and neck with great cyanosis, great respiratory difficulty simulating an acute and violent attack of asthma, prostration and collapse.

It may be mentioned here that the most serious symptoms which have occurred in man, and the individuals who for the most part have succumbed, do so after the first injection of foreign protein. These individuals, as far as can be learned, have not received previous injections of the specific proteins to which they react and have been termed naturally hypersensitive individuals.

The numerous studies which have been made upon the physiology, pharmacology and chemistry of anaphylaxis have resulted in an enormous amount of work, and no attempt will be made here to present a comprehensive review of this subject nor to discuss the various theories regarding the mechanism of sensitization or of shock. Several reviews of the subject and extensive bibliographies are readily available, and the object of this chapter is to present a description particularly of the disturbances of metabolism, that are precipitated or associated with anaphylaxis and allied phenomena.

It need only be pointed out that the physiological studies upon animals suffering from anaphylactic shock have shown that changes take place in different structures and different organs, the localization varying somewhat in the several species of animals that have been investigated.

The important studies of Auer and Lewis first showed the effect

produced upon the lung of the guinea-pig during the anaphylactic shock. They proved conclusively that the great distention of the lung found at autopsy and the respiratory symptoms accompanying the shock during life were dependent upon a constriction of the smooth muscles of the bronchioles. The asphyxia which is caused by this extreme contraction is immediately responsible for the death of the animal in acute shock. In the guinea-pigs that survive for some time after the onset of symptoms, the marked distention of the lungs and the bronchiospasm are not obvious, and may even be absent. In these animals hemorrhages are frequently found over the pleura and in the lung itself. The extraordinary bronchial spasm so characteristic of anaphylactic shock in guinea-pigs has not been found in other animals that have been subjected to experimentation. In the rabbit it seems probable that, though the bronchial musculature escapes, the walls of the smaller arteries are constricted and so narrowed that they greatly impede the pulmonary circulation and are directly responsible for the death of the animal. Schulz(*b*) has offered some evidence to show that this may also occur in the cat.

The cardiovascular mechanism is profoundly affected during both acute and subacute shock. It was shown first by Biedl and Kraus(*a*) that, in the dog, a profound drop in blood pressure takes place. This abrupt fall in blood pressure which is so characteristic of shock in dogs occurs apparently in one form or another in anaphylactic shock in all animals upon which experiments have been done so far and has, too, been observed in man. In the dog the fall is usually very abrupt, whereas in the rabbit and in the guinea-pig the lowering of blood pressure may be slower and more protracted and is generally preceded by a very temporary but distinct rise. The changes in blood pressure, in the dog at least, are not dependent upon primary cardiac failure, as has been definitely demonstrated by Pearce and Eisenbrey(*a*)(*b*), but are probably dependent upon changes in the peripheral circulation and are analogous to the low pressure which occurs in surgical shock.

Though there has not been any definite evidence forthcoming to show that the capillaries themselves are disturbed during anaphylactic shock, collateral observations have been made which suggest that this important portion of the peripheral circulation may undergo changes which hitherto have been unsuspected. The recent work of Dale and Laidlaw(*a*)(*b*) and Dale and Richards has indicated first that in histamin poisoning in cats, evidence is obtainable in favor of the view that there occurs a general loss of tone by the capillaries throughout the body, and that the excessive permeability of these vessels, which allows escape of plasma, may be regarded as an important factor in the production of histamin shock. They demonstrated further by appropriate experiments that, though histamin contracts the fine arterioles, there is a fall of blood pressure in histamin shock and show that this is due to a dilatation of the capillary

bed. In order to bring about this capillary dilatation, the capillaries themselves must previously be in tone. They bring forward evidence thus to show that the capillaries, far from being passive agents, take a very active part in the circulation and are dilated by the direct toxic action of histamin upon them. They finally discuss the relation of the condition observed in histamin shock to that which may be present in anaphylactic shock. Bearing upon this question are the important observations of Krogh(*b*), who has shown that after stimulation of voluntary muscles, great numbers of capillaries which in the resting muscle are practically invisible become functionally active. In a single area of muscle not only is the capillary bed greatly increased, but at times the diameters of the capillaries already functioning are widened. Indeed, exactly this condition has been observed to occur in the omentum of the rabbit following both the direct application of histamin to the omentum and after the injection of this substance intravenously. The dilatation of the capillaries of the omentum, moreover, precedes by a measurable interval the drop in blood pressure and therefore seems almost certainly to be the cause rather than the effect of this phenomenon so characteristic of histamin shock. These observations make it seem highly probable that an analogous condition may exist during anaphylactic shock and indeed Weil(*h*) has made the observation that the injection of horse serum into the liver of a dog sensitized to this protein results in a local engorgement of the organ in this region.

The heart, however, does show a number of functional changes during the reaction. Auer and Lewis first observed that auriculoventricular dissociation occurred in guinea-pigs succumbing to anaphylactic shock, resulting often in partial or even complete heart block, while more complete study by Auer and Robinson(*a*)(*b*) showed that a variety of alterations in the character and sequence of the heart beat were to be observed, both in rabbits and in dogs which were subjected to anaphylactic shock. Though several alterations in the electrocardiographic curves were noted, the most important were the partial and complete blocks which occurred in these animals. In the dog it is more customary to find merely a lengthening of the P-R interval, but occasionally auriculoventricular dissociation may be observed in this animal. Schulz(*b*), too, has noted cardiac irregularity in cats and has commented upon the auriculoventricular dissociation that occurs. He likewise states that in these animals there is an enormous engorgement of the right side of the heart and the pulmonary artery, while the left side of the heart is practically empty. Together with this the peripheral vessels are constricted.

In connection with the phenomena of anaphylaxis in dogs an interesting observation was made by Calvary, who by quantitative estimations, found a great increase in the lymph flow independent of the changes in blood pressure.

That changes occur in the gastrointestinal tract is evidenced by many

of the symptoms that occur during acute and chronic anaphylactic shock, and it has been found on observation, indeed, that in practically all animals studied, peristalsis of the small intestine is greatly increased.

Although the liver seems to be unaffected in typical anaphylactic shock in sensitized guinea-pigs, rabbits and cats, this organ plays an important part in anaphylaxis of the dog. Manwaring was the first to call attention to this fact and stated that removal of practically all the viscera, except the liver, of a dog sensitized with horse serum does not prevent the occurrence of a pronounced drop in the blood pressure when this animal is reinjected with the protein to which it has been sensitized. If, however, the liver alone is excluded from the general circulation, the characteristic drop in blood pressure can usually be prevented. Voegtlin and Bernheim corroborated Manwaring's experiments, and by employing sensitized Eck-fistula dogs, showed that when the portal vein near the hilus of the liver and the hepatic artery were clamped, reinjection of horse serum did not produce a fall in pressure. When the clamp was removed and the circulation in the liver re-established the blood pressure fell rapidly. They also demonstrated that if the Eck-fistula was performed before the first injection of foreign protein, the animal, on reinjection, rarely showed the symptoms of anaphylactic shock, suggesting that the Eck-fistula in some way had interfered with sensitization. Denecke has confirmed these experiments, using egg-white, and concludes that in the dog the liver is necessary both for sensitization and for the production of anaphylactic shock. Weil, too, has pointed out the importance of the liver in the symptomatology of anaphylactic shock in dogs and has shown that during the period of shock the liver is enormously engorged with blood. Simmons in a recent note has pointed out the fact that in the dog the hepatic vein has a rich musculature, and suggests that during anaphylactic shock these vessels may undergo marked constriction.

The most important alterations in the blood and blood-forming organs are to be observed in changes in the coagulability of the blood and in the cellular constituents. The fluidity of the blood and marked delay in coagulation during anaphylactic shock, which Biedl and Kraus(*a*) observed in their early experiments upon dogs has been noted quite regularly in most species of animals dying of acute shock. According to Sirensky this is dependent upon the diminished fibrinogen content of the serum. Pepper and Krumbhaar concluded from a study of the delayed coagulation of the blood in anaphylactic dogs that the diminished coagulability was dependent upon either a decrease in thromboplastin or an excess of antithrombin.

Lee and Vincent believed that they could show in guinea-pigs that anaphylactic shock caused an injury to blood platelets which are rich in thromboplastic substance. In serum disease in man, a decrease in coagulation time may occur, but that actual purpura may develop during serum sickness without change in coagulation time, bleeding time, or number of

platelets is evident from a case reported by Meleney. There has been as little uniformity in the technique employed as in the results obtained so that a definite statement as to how the delay in coagulation is brought about must await further investigation. In a paper by Shattuck will be found reference to the more important studies on this problem.

The cellular reaction observed by v. Pirquet and Shick in serum disease in children consists in a preliminary leukocytosis, with increase in polymorphonuclear leukocytes and, later, a leukopenia with well-marked relative increase in the lymphocytes. In animals, apparently the characteristic reaction of acute shock consists in a marked leukopenia, followed, when recovery ensues, by a moderate polymorphonuclear leukocytosis and a return to normal within 24 to 48 hours. In acute shock, an increase in the eosinophile cells of the blood is not observed, but after repeated local injections of a foreign serum, Schlecht and Schwenke have observed local collections of eosinophilic leukocytes, and Rackamann has noted variations in the cellular reaction of the peritoneal fluid of the guinea-pig.

It will be seen from what has already been said that the action of the poison producing anaphylactic shock is directed towards the smooth muscle of various portions and organs of the body and that many of the symptoms, though they vary in different species, are dependent upon the contractions or dilatations of the smooth muscles of the bronchi, of the walls of the intestines, and of the blood vessels in such organs as the lung and the liver. Definite proof of this action was first brought forward by Schulz and later by Dale and his co-workers. They have shown that the cornu of the uterus of a virgin guinea-pig sensitized to a specific protein reacts specifically by characteristic contractions, when it is brought in contact outside of the body with the protein to which the guinea-pig has been sensitized. This reaction has been found to be highly delicate and sensitive and occurs when the smooth muscle has been washed free of all blood and body fluids. Under the conditions of the experiment the reaction, moreover, is highly specific, and the characteristic contraction cannot be obtained, either by the addition of the guinea-pig's own serum or by proteins other than that to which the guinea-pig has been sensitized. The same principles, moreover, hold for the reactions of the muscle strip as obtain for the anaphylactic reactions in the guinea-pig, for it is possible to desensitize the smooth muscle by the additions of protein up to the normal limit of contraction. After the muscle strip has been treated in this manner it no longer reacts when bathed in the specific serum. Not only is this specific reaction obtained with the smooth muscle of the uterus from actively sensitized guinea-pigs, but it may likewise be demonstrated after the passive sensitization of a guinea-pig when the strip of washed smooth muscle will react characteristically if suspended in fluid to which the specific protein has been added. The sensitiveness of the smooth muscle, after active sensitization, appears on the 6th to the 8th

day and increases up to the 12th day. To the same end, Dale showed that, when the washed sensitized guinea-pig's lung is perfused with a fluid containing the specific protein to which the animal has been sensitized, contraction of the bronchial musculature occurs and gives rise to the acute distention of the lungs, which typifies the anaphylactic shock reaction in the living guinea-pig. Still further amplifications of these experiments have been made by Weil and by W. H. Manwaring, Y. Kusame and H. E. Crow. Weil, moreover, has shown that this specific reaction may be obtained in the smooth muscle of the Fallopian tube from the human being who has been sensitized artificially to horse serum, thus demonstrating that the same mechanism pertains to this reaction both for the experimental animal and for man.

Etiology.—The etiology and place of formation of the poisonous substance which brings about the anaphylactic shock has received much discussion, has been extensively investigated and still remains in many essential regards unsatisfactorily explained. Even with the knowledge afforded by numerous experiments, the place of formation of the poisonous substance which brings about the symptoms of anaphylactic shock is still under considerable discussion.

The two theories which have been most ardently adhered to are the cellular and humoral theories. The adherents of the first theory, represented especially by Dale, Laidlaw, Schulz, Weil and others, have brought forward not only the evidence mentioned in the preceding paragraphs to uphold the view that the reaction in anaphylactic shock and the formation of poisonous substances takes place within the cells of the body, but have emphasized other factors which are important links in the argument. It is known, and has been demonstrated and emphasized by Weil and others, that, in order to obtain passive sensitization in the guinea-pig, an appreciable time must elapse between the injection of the foreign protein and the development of passive sensitization of the animal. The injection of a normal guinea-pig simultaneously with serum from a sensitized guinea-pig and with the specific protein has not, except in extremely rare instances, brought about anaphylactic shock. It is necessary, as has been repeatedly shown, that a period of 4 to 6 hours at least elapse before the condition of sensitiveness in the guinea-pig appears and that during the next 12 to 24 hours, the degree of sensitiveness increases. Once having been established, it persists in the guinea-pig for several days, although the period of passive sensitiveness in the rabbit, according to Friedemann, lasts not longer than 24 hours. The assumption is that there must be an interval between the injections of the serum from the actively sensitized animal and the injection of the specific protein into the passively sensitized guinea-pig, in order that the anaphylactic antibody may unite with the cells of the body and render them sensitive to the subsequent injection of the specific protein.

There can be no doubt that the evidence which has been brought forward is sufficient to demonstrate clearly that an important part of the reaction during anaphylactic shock is intracellular in nature and is dependent upon the formation of some toxic substance or reaction in the body cells and especially the smooth muscle cells.

But whether this is the only method by which the intoxication takes place is still questioned by the adherents of the humoral theory. The striking resemblance between the anaphylactic shock and the intoxication produced by the injection of certain protein derivatives formed originally the basis for the humoral theory of the nature of anaphylactic shock. The early demonstration of de Waele and Biedl and Kraus that products of protein digestion, such as peptone and products of proteolysis, produce effects in animals very similar to anaphylactic shock, led to an enormous amount of work in an attempt to demonstrate that such products were formed by splitting of protein in the blood of the animal during anaphylactic shock and resulted in the typical intoxication. The work of Vaughan showing that such substances might be obtained from bacteria by proteolysis, and the demonstration by Friedberger(*b*) of so-called anaphylatoxin which could be produced outside the body by the digestion of serum and the bodies of bacteria, both led to the support of this hypothesis. In general three hypotheses as to the formation of these toxic substances in the blood have been advanced and have formed the basis of much experimentation, though all depend for their explanation of the phenomenon upon the assumption that a union takes place between the circulating antigen and antibody, with the formation of a toxic substance either from the antigen or from the body fluids of the animal. The theory advanced by Jobling, Peterson and Eggstein(*a*) assumes that the union of antibody and antigen removes the antitryptic factor in the blood, releases the tryptic ferment, and thereby initiates cleavage of the blood proteins and the production of toxic substances. Another theory which has been brought forward and been the subject of an extremely interesting series of experiments by Novy and De Kruif regards the union of the antigen and antibodies as disturbing the delicate equilibrium of the plasma colloids which initiate changes that allow the blood to become toxic.

There are innumerable experiments which go to show that the serum of animals may be rendered toxic either for the same species or for different species by a great variety of manipulations. Thus, incubation of a normal serum with a specific precipitate formed by the interaction of precipitin and precipitinogen results in the formation of a toxic substance (anaphylatoxin). In the same way, normal serum incubated with an emulsion of living or dead bacteria or with such inanimate substances as kiesselguhr with kaolin or with the sols of agar-agar, with heat-coagulated protein or even by shaking with chloroform will render it toxic. In the experiments of Novy and De Kruif the toxicity of the serum often ap-

peared in waves. It has also been amply demonstrated that the toxic substance formed by manipulating the serum in this manner *in vitro* produces symptoms when injected into animals such as the guinea-pig that are analogous to anaphylactic shock, but, so far, there are no convincing experiments to show that the injection of these inert substances into the normal animal react with the serum of that animal *in vivo* to form the toxic substances so readily obtained *in vitro*. It is true that injection into the circulation of guinea-pigs of various inert or colloidal substances such as agar, kaolin, starch or inulin call forth symptoms that simulate anaphylactic shock, but Hanzlik and Karsner after experimentation with these substances and a long list of others such as arsphenamin, collargal, gelatin, acacia and peptone which produce what are known as anaphylactoid symptoms, come to the conclusion that the mechanism of their toxic action is different from that observed in anaphylactic shock. Death of the animal in some instances and particularly after the use of agar is due to pulmonary thrombosis, or, in other instances, is associated with pulmonary hemorrhages, hemolysis or a direct toxic action upon the tissues of the body. Further observations upon the inhibition of symptoms by atropin or adrenalin, upon lung perfusion and muscle strip tests, convince them that the toxic effect of these substances has no bearing on anaphylaxis and should not be confused with it.

There is, perhaps, one outstanding exception to the negative results which have so far been reported, namely, those of Bordet upon anaphylaxis with erythrocytes. Bordet has shown that the simultaneous injection of erythrocytes together with their specific anti-serum in the normal guinea-pig will bring about a reaction which simulates the active anaphylaxis caused by the injection of red cells in sensitized animals, and he therefore concludes that the toxic substance which produces these symptoms is, under these circumstances, formed in the circulation.

In reviewing the evidence so far brought forward in support of these various theories, one must come to the conclusion that in anaphylactic shock, the cells of the body play an important part in the process. Though most of the positive experiments show that the toxic reactions take place within the cells and are independent of the formation of any poisonous substance in the blood of the animal, still, it is not altogether possible to exclude humoral reactions as aiding in, or playing some part in, the production of the intoxication.

Whatever the origin of the toxin and wherever the point of attack in the body, there is considerable evidence to show that profound changes take place not only in the metabolism of the cells but in the chemistry of the body fluids. Whether some of these changes are the cause or the effect of anaphylactic shock can not at the present time be ascertained, though it seems probable that many of them must be considered at least as a part of the abnormal reaction.

Pathology.—The careful studies that have been made upon the pathology of the tissues following acute shock have thrown but little light upon the subject. Hemorrhages into the lung and beneath the epicardium in guinea-pigs were early described by Gay and Southard(*a*)(*c*). The guinea-pig that recovers, however, from a single non-fatal anaphylactic shock shows no permanent traces referable to these lesions. More recently, however, the observations of Beneke and Steinschneider and Worzchowsky and Kundratitz and Auer have indicated very definitely that, following an acute anaphylactic shock, both in the guinea-pig and in the rabbit, there occur degenerative lesions in the heart muscle which consist in swelling and granulation of the fibers and a condition which Auer particularly has described as a hyalinization of the muscle fibers.

In rabbits, as was originally shown by Arthus, repeated injections of serum made subcutaneously give rise to a local edema, hemorrhage or necrosis that usually appears after the third or fourth inoculation. This reaction has been shown more recently by Schlecht and Schwenke to be characterized particularly by an exudation of mononuclear cells and eosinophilic leukocytes into the tissues. A somewhat similar localized reaction has been described by Friedberger and Mita and by Ishioka, following the intratracheal insufflation of horse serum in sensitized guinea-pigs and termed by them an anaphylactic pneumonia. Under these circumstances, an inflammatory reaction is instituted in the lung and gives rise, according to these authors, to two types of pneumonia. Most frequently there is proliferation of epithelial cells from the alveolar walls, followed by an exudate containing fibrin into the alveoli, whereas, in the second type, the cellular reaction is largely confined to the alveolar walls themselves.

Repeated anaphylactic shocks in guinea-pigs, rabbits, dogs and cats may produce, as has been shown by Longcope and Boughton, necrosis in the heart muscle, the liver and the kidneys which result in a subsequent local inflammatory reaction with infiltration of small, round cells. The recent observations of Auer(*c*) upon the local reaction in the ears of sensitized rabbits re-injected with horse serum, have an important bearing upon the influence of pre-existing injury upon the localization and severity of these focal reactions, for he found that, when the ears of rabbits were inflamed by the application of zylol, extensive edema and necrosis occurred at the site of the inflammatory reaction when sublethal doses of horse serum were injected intravenously and explains this phenomenon on the assumption that the antigen escaped from the circulation into the tissues at that region and set up there a reaction simulating that originally described by Arthus. It is known, too, through the work of Gay and Lucas, that similar local reactions may occur in children who receive, at approximately weekly intervals, horse serum in the form of diphtheria antitoxin, as this substance is employed for preventive measures.

There is, therefore, considerable evidence to show that the anaphylactic shock or the repeated injections of foreign protein in animals and in man are accompanied, or followed by, definite changes in some of the tissues of the body.

Protein Metabolism in Anaphylaxis.—Not only have there been observations upon the tissue changes but a considerable number of investigators have directed their attention to a study of the chemistry of the body, to determine whether there are evidences of disturbed metabolism. With the development of the theory that the intoxication was dependent upon the formation of products of protein disintegration, numerous attempts have been made to demonstrate chemically the occurrence of these substances in the blood and tissues during anaphylactic shock. The early experiments of Friedmann and Isaac, who used egg-white as antigen, pointed to the fact that when doses of 5-100 c.c. were used in dogs and goats, nitrogen excretion was increased in the sentitized animals as compared to the normal controls. Schott and Heilner and Hirsch, however, failed to find any increase in protein metabolism. In a more recent study of this question Major has brought forward evidence to show that, immediately after anaphylactic shock there is often, though not constantly, a fall in nitrogen excretion. When rabbits are employed, these animals frequently become ill 5–10 days after the intoxicating dose, and during this period there is a definite increase in the nitrogen excretion, at which time the animal loses weight. The loss of weight, both after acute shock in rabbits and after repeated injections of foreign protein, has been frequently observed, but Major considers that this is partly due to the fact that the animals are likely to take less food. This fact casts some doubt upon the relation which the increased nitrogen output in the urine has to the previous anaphylactic shock, for it seems possible that at the time the nitrogen increase appears in the urine, the animals have exhausted their available carbohydrate and fat, and are burning their own tissue proteins.

The results of Manoiloff, however, supplied some confirmatory evidence for the work reported by Friedmann and Isaac. Using rabbits, he found that after anaphylactic shock, there was a rise in urinary nitrogen, and then gradually a return to normal at the end of two to two and a half weeks. Furthermore, on the basis of biological tests (specific precipitin reactions) he concluded that the increase in nitrogen output was not due to excretion by the kidneys of the protein injected. In our laboratory this observation has been repeatedly confirmed in studying the fate of horse serum administered therapeutically in lobar pneumonia and meningococcus meningitis. We have never been able to demonstrate horse serum in the urine of these patients by precipitation with immune rabbit serum. Schittenhelm and Weichardt also confirmed the results of Friedmann and Isaac, reporting an increased nitrogen

output after anaphylactic shock in dogs. Segale, too, found increased nitrogen excretion after reinjection of sensitized animals—an increase which continued for three days. Leschke(*a*)(*b*) also investigated this question, studying particularly the nitrogen metabolism, gas exchange and temperature reactions in anaphylaxis. Using Friedberger's anaphylatoxin, he administered to dogs sufficient amounts to produce symptoms but not death. Animals treated in this way showed no evidence, judged by the urinary nitrogen, of increased protein metabolism. Further experiments with active anaphylaxis yielded similar results. He concludes that the anaphylactic poison primarily depresses protein metabolism and total metabolism, and that this depression occurs no matter whether there is a rise or fall of body temperature after the intoxicating dose. He criticises the results of Manoiloff and Segale on the ground that these investigators ignored the effect on the protein metabolism of the concomitant phenomena—motor activity, spasms, convulsions, respiratory and circulatory disturbances. He holds that the evidence of accelerated protein metabolism obtained by Segale and Manoiloff was due to these phenomena of the reaction and not to any direct action of the anaphylactic poison. The validity of this criticism is questionable. Unless the fat and carbohydrate stores of the body are exhausted by starvation or exercise, or for some other reason become less available, motor activity, unless long continued, does not increase the combustion of protein. Pettenkofer and Voit first demonstrated this fact, and later it was confirmed quite conclusively by Krummacher. Kocher, indeed, states that doubling the heat production of the day as by walking 60 kilometers has little or no influence on the protein metabolism of man. The method of sensitization used by Leschke, furthermore, makes it seem probable that his animals were in a state of anti-anaphylaxis during the test period.

It is apparent from these discordant results obtained by different workers in studying the disturbances of protein metabolism during anaphylactic reactions that there must be unrecognized sources of error. Leschke himself emphasizes the possibility of variable effects according to the size of the sensitizing dose, the interval between sensitizing and intoxicating doses, the amount of antibodies formed, the size of the reinjection dose and the method of administration. But there is another important objection to which the investigators whose work we have referred to have given scant or no attention. All their conclusions were based on studies of urinary nitrogen only, apparently with the assumption that renal function was undisturbed. To what extent renal function also was affected by the lesions observed by Longcope and Boughton after repeated anaphylactic shocks was not studied, but with such marked anatomical changes it is highly probable that function also was impaired. Such being the case, one should be cautious in drawing conclusions regarding protein metabolism after reinjection of animals sensitized by repeated doses of a foreign

protein, if the possibility of retention by damaged kidneys has not been eliminated.

It is therefore important to consider the studies of protein metabolism in which the factor of renal function is not involved. Investigators seeking to discover the ultimate anaphylactic mechanism have helped to solve this problem of nitrogen metabolism in anaphylaxis. Manwaring's important series of experiments, referred to above, on the reaction of the tissues and organs concerned in protein digestion and assimilation first drew attention to the crucial part which the liver plays in canine anaphylactic reactions. Manwaring found that "if temporary sutures are placed around the aorta and vena cava, above the diaphragm, the upper half of the anaphylactic body will not react to a serum injection. The supradiaphragmatic tissues and organs, therefore, are not primarily concerned in anaphylaxis." Release of the ligatures is followed by typical shock. He removed all the abdominal viscera, except the liver, and the sensitized animal still responded to reinjection by typical shock. "We are therefore forced to conclude," he says, "that the essential primary organ is the only remaining viscus, the liver." Further work seemed to indicate that the intestines and attached pancreas constitute a second primary anaphylactic mechanism. In the light of these results the contribution of Hashimoto and Pick is interesting. They found that the non-coagulable nitrogen in the livers of normal guinea-pigs forms about eight per cent of the total nitrogen. In the livers of sensitized animals they found that the non-coagulable nitrogen formed about 22 per cent of the total nitrogen. In the kidneys, brain, spleen and blood they found no such differences between normal and sensitized animals. They found, too, that following the sensitizing dose, the percentage of non-coagulable nitrogen of the liver increased up to the fourteenth day and then decreased. Interesting as these results are, they require confirmation, because Barger and Dale(*b*), in an effort to confirm them, used the same technic and could detect no noteworthy difference between normal and sensitized animals so far as the non-coagulable fraction of the total nitrogen was concerned. Experiments of the same type were done by Auer and Van Slyke. They determined the amino nitrogen content of the lungs of guinea-pigs after anaphylactic shock. No significant difference between anaphylactic and control guinea-pigs could be demonstrated. Moreover, they showed that fluctuations in the amino nitrogen figures amounting to one-third of that present may occur in animals kept under approximately the same conditions.

Recent work by Rumpf has supplied evidence indirectly confirming the results of Manwaring's work on the site of the anaphylactic reaction and at the same time has supplied additional support for the cellular theory of anaphylaxis. In perfusion experiments on the excised livers of sensitized and normal guinea-pigs, he studied the urea formation with and without the addition of specific antigen. His results are summarized as

follows: (1) The amount of urea formation in both normal and sensitized animals corresponds to the weight of the animal. Urea formation was found to continue, under the conditions of the experiment, for at least an hour and a half after excision. (2) Normal livers, upon the addition of serum, showed no diminution of urea formation. (3) Livers of anaphylactic pigs, however, while showing normal urea formation before the antigen was added to the perfusion fluid, appeared to lose completely the power of urea synthesis, when the antigen was added. (4) If the serum was added drop by drop so as to produce anti-anaphylaxis, no inhibition of urea-synthesis occurred.

An investigation of the nitrogen of the blood in anaphylaxis and peptone poisoning reported recently by Hisanobu fails to confirm Rumpf's results unless we assume that the increase of blood urea in serum anaphylaxis, reported by Hisanobu, is due to extrahepatic urea synthesis. Besides an increase of blood urea, Hisanobu also found that there was a rise during anaphylactic shock of the total non-protein nitrogen, the "rest" nitrogen and the amino nitrogen. Figures for all these substances in peptone shock were intermediate between those found in control pigs and pigs with serum anaphylaxis. This is in agreement with results obtained by Whipple and Van Slyke(*b*) in studying the effect of proteose intoxication upon the nitrogenous products of the blood. We shall refer later to the effects of peptone injections on metabolism in connection with a discussion of the alteration of temperature regulation caused by anaphylactic reactions. It is pertinent, however, to recall here the fact that Mendel and Rockwood had already shown that parenteral introduction of edestin was followed by increased nitrogen elimination in excess of the amount of nitrogen injected.

It can scarcely be doubted that the reaction of a sensitized animal to reinjection of the specific antigen entails significant changes in protein metabolism, but at the present time the evidence is so conflicting and so many phases of the problem are still uninvestigated that any comprehensive statement concerning nitrogen metabolism in anaphylaxis is impossible. The weight of evidence points to an increase of the end products of protein metabolism in both the urine and circulation and therefore supports the assumption that the anaphylactic reaction is associated with an increase in protein katabolism. It seems probable also that with this quantitative change, there also is a qualitative alteration in protein metabolism, so that during anaphylactic reactions, nitrogenous substances not normally formed are elaborated.

Respiratory Metabolism.—The question of gas exchange in the anaphylactic reaction was first studied in England by Scott and in Germany by Loening. The former found that with an experimental error of 5 per cent, the output of CO_2 fell 35 per cent in animals subjected to passive anaphylactic shock. In active anaphylaxis, when the symptoms were slight

the results were negative. In some experiments, in which most of the animals showed only mild symptoms, the diminution of CO_2 excretion averaged 25 per cent. Loening's more comprehensive study on guinea-pigs and rabbits demonstrated that in anaphylactic shock the fall in body temperature was dependent upon diminution in combustion processes. That, at least, is the most plausible interpretation. The diminished O_2 intake and CO_2 excretion are due, he states, not to any disturbance of heat dissipation, but to an actually lowered heat production resulting from "Nachlassen in der Verbrennungsenergie." These results were confirmed by Leschke, who found in rabbits in which he produced anaphylatoxin fever, a decrease both in O_2 intake and CO_2 output without change of the R. Q. Similar results were obtained with dogs. In anti-anaphylaxis, he failed to demonstrate any alteration in either temperature or metabolism.

Heat Regulation.—To Pfeiffer belongs the credit of first calling attention to the significant alterations in body temperature which accompany the response of a sensitized animal to reinjection of the specific protein. Krehl(*b*), to be sure, first described the temperature effects of the parenteral administration of foreign protein in a normal animal. He showed that fever follows the injection of small doses while a fall in body temperature results from the introduction of large quantities. He and Matthes, even before Richet reported his discovery of anaphylaxis, were struck by the fact that animals which had previously been injected with foreign protein reacted with a higher temperature upon reinjection. A similar observation had, indeed, been made by Buchner while studying the fever-producing action of bacterial proteins. None of these workers, however, appreciated how close he was to the fundamental fact of anaphylaxis. Pfeiffer pointed out the specificity of the reaction in both active and passive anaphylaxis, and showed besides that it is not demonstrable before the development of the anaphylactic state, that it may be elicited by both the intraperitoneal and intravenous injections, and that by means of it, the non-specific anti-anaphylaxis produced by peptone (Biedl and Kraus) is confirmed. He considered it the most delicate and most accurately measurable symptom of anaphylactic shock. Abundant and incontestable confirmation of the essential features of Pfeiffer's observations soon appeared, but at the same time, certain limitations to this method of measuring anaphylactic reactions were definitely demonstrated. Loewit agreed with Pfeiffer that when animals were reinjected with small doses and did not die in acute anaphylactic shock, that there is temperature drop, but in guinea-pigs with "blizenartig" shock and quick death, he found no definite fall of temperature as part of the reaction. An interesting contribution to this question of the temperature reaction in anaphylaxis was made by Friedberger and his co-workers. They demonstrated quite definitely that the sensitized animal and the normal animal reacted to the injection of foreign protein in much the same way *qualitatively.*

In both the normal and hypersensitive animal the dose can be so graded as to produce either a rise or a fall in temperature, and between the two, a dose can be found which produces no temperature change. But between the normal and hypersensitive animal there is a striking *quantitative* difference. In guinea-pigs, for example, the hypersensitive animal shows the temperature reaction after 1-500,000 to 1-1,000,000 of the dose producing the same type of temperature reaction in the normal animal. Schittenhelm, Weichardt and Hartmann and Leschke cited experiments confirming with rabbits and dogs these observations made on guinea-pigs. Of considerable interest in this connection is the work of Friedmann and Davidson on the temperature reactions following injections of sodium chlorid. Using a 0.75 per cent NaCl solution, they found that rabbits in the anaphylactic state reacted more sensitively, judged by the temperature reaction, than normal animals. Normal rabbits injected subcutaneously with 5 c.c. to 23 c.c. per kilo showed fever for a day. A smaller dosage than this caused no change in temperature. Anaphylactic animals, on the other hand, reacted when 2 c.c. to 5 c.c. per kilo were injected. Moreover, in the anaphylactic animals, the reactions come on within two to three hours after the injection, while in the normal animal no temperature change is observed for six to eight hours.

We have already referred to the experiments of Leschke on the gas exchange and temperature reaction of anaphylactic animals and to his conclusions that with anaphylaxis there comes a depression of the intracellular combustion processes. If this be true, then we must assume that in those reactions to reinjection in which there is a rise of temperature that some additional mechanism comes into action. If less heat is being produced at the time the temperature is above normal, there must be some disturbance of the mechanism of heat loss. Perhaps the results of Hirschfeld, who found a vasoconstrictor substance in the serum and plasma of anaphylactic pigs, will prove to be of some significance in this connection. Nevertheless, opposed to this are the experments of Pfeiffer and Jarisch, who were able to abolish the temperature drop of anaphylactic shock by administering barium chlorid, the vasoconstrictor action of which presumably lessens heat loss. Pfeiffer and Jarish concluded from this barium chlorid effect that the assumption of diminished heat production in anaphylactic reactions was untenable. We know from Weil's(*h*) studies, that there is a vasomotor depression with marked engorgement of the liver in canine anaphylaxis. Theoretically, therefore, it is possible to explain the different temperature reactions after reinjection of hypersensitive animals by varying degrees of participation of four factors—heat production, peripheral vasoconstriction, internal vasomotor depression, and alterations in blood-pressure.

Serum and Cellular Ferments.—One of the most interesting phases of the pathological physiology of anaphylaxis is the question of the part

played by serum and cellular ferments. It is of fundamental importance from the theoretical viewpoint; indeed most conceptions of the mechanism of the anaphylactic reaction with the exception of those which base it on physical changes, involve the fundamental idea that the poison causing the symptom of anaphylaxis is produced by protein cleavage mediated by ferments.

Friedmann and Isaac, on the basis of increased nitrogen excretion after reinjection of sensitized animals, assumed the formation of a proteolytic ferment as a result of the sensitizing injection. Heilner(*b*) was led to the same assumption from the same type of evidence. Other observations pointing to a ferment action were:—first the demonstration by Friedberger(*b*) that anaphylatoxin is formed *in vitro* by the action of anti-serum, antigen and complement (it is now known, however, that the anaphylatoxin is also produced by the action of agar or kaolin on normal serum); secondly, the work of Vaughan on the toxic fraction of the protein molecule, formed by alcohol-alkali hydrolysis of protein, with action similar to the anaphylactic poison; and thirdly, the demonstration by Biedl and Kraus, and Pfeiffer and Mita, that injections of peptone produce symptoms similar to anaphylactic shock.

With evidence of this type, investigators naturally set to work to demonstrate a ferment for the protein used in sensitization. Almost simultaneously, Abderhalden and Pincussohn, and Pfeiffer and Mita reported a proteolytic ferment which accumulates during the preanaphylactic stage, diminishes during shock and anti-anaphylaxis, and then appears again later in increased amount. Pfeiffer and Jarish later confirmed these results with the dialysis method of Abderhalden. They found that the proteolytic power is present on the sixth day and persists 30 to 40 days. They also demonstrated the proteolytic power in passive anaphylaxis, but found that in anti-anaphylaxis it is lost for three to four days. Furthermore, their results seemed to show that the smallest amount of antigen giving rise to ferment formation, corresponds closely to the minimal sensitizing dose as shown by the temperature drop after reinjection. Zunz and Gyorgy confirmed much of this work, using the accurate Van Slyke method to determine amino nitrogen production in mixtures of serum from a sensitized animal and the specific antigen.

The results of Jobling and Petersen and Eggstein, while agreeing in some particulars with the conclusions just cited, contain points of disagreement. They reached the following conclusions regarding serum ferments in anaphylaxis:—(1) The ferments are practically unaltered by the primary injection of foreign protein. (2) During the course of sensitization, the injection of antigen is followed by mobilization of a non-specific protease, and the mobilization increases in intensity and rapidity as the maximum period of sensitization is reached. (3) Acute shock is accompanied by: (a) instantaneous mobilization of a large amount

of non-specific protease; (b) a decrease in anti-ferment; (c) increase in the non-coagulable nitrogen of the serum; (d) increase in amino acids; (e) decrease in serum proteose. (4) Later there is a progressive increase in the non-coagulable nitrogen, proteose and lipase of the serum. From these experimental results, they formulate a theory of the mechanism of anaphylactic shock which departs from current conceptions. They believe that acute intoxication is brought about by the cleavage of serum proteins, including proteoses, through the peptone stage by a non-specific protease. The least convincing part of their argument is the explanation offered for the specificity of anaphylactic reactions. They say, "The specific elements lie in the rapid mobilization of this ferment and the colloidal serum changes which bring about the change in anti-ferment titre."

The aim of these studies was to elucidate the problem of the mechanism of anaphylaxis, and even though they may not suffice to clear this difficult problem, they are nevertheless of importance from the point of view of the metabolic disturbances associated with anaphylactic phenomena.

If serum be added to a mixture of a protein and a proteolytic enzyme, present in the mixture in such proportions that the enzyme will completely hydrolyze the protein, the anti-proteolytic power or antitryptic titre of the serum is manifested by the extent to which hydrolysis of the protein is inhibited. If an anti-proteolytic substance be present in the serum unsplit protein will be present when equilibrium is reached.

So far as we are aware, the earliest attempt to bring alterations in the anti-ferment titre into relation with anaphylaxis was made in 1912 by Ruszniak. Sensitizing guinea pigs with egg white and allowing an incubation period of 2–4 weeks, he withdrew blood about 15 minutes after the reinjection. He found that in normal animals, the anti-ferment titre was 40–50, while in anaphylaxis it was 70–110. On the basis of the demonstration by Bayliss that split products inhibit the action of specific ferment on account of the reversibility of the enzyme reaction, and absorption of the ferment by split products, Ruszniak offers his results as further evidence of protein cleavage in anaphylaxis. Rosenthal, indeed, brought forward evidence that the normal antitryptic power of the serum is dependent upon the amino acids present.

The results of Ruszniak, even though they are in harmony with conclusions reached by others and theoretically are plausible, cannot be accepted without confirmation; especially because both Seligman and Ando, each using a technique almost identical with that of Ruszniak, failed to find any increase in the anti-ferment titre of the serum.

Non-Specific Alteration of the Degrees of Hypersensitiveness.—Owing to the obscurity which still surrounds to a large extent the mechanism of anaphylaxis, the mode of action of those substances which

increase or decrease susceptibility is for the most part unknown, but from a theoretical as well as a practical standpoint, considerable importance is attached to the procedures which alter in either direction the susceptibility of the sensitized animal to reinjection.

Whatever be its mode of action, the fact has been demonstrated that if quinin be injected before the intoxicating dose of antigen, the minimal lethal dose is reduced and the symptoms from a sublethal dose are more severe than in control animals untreated with quinin. Smith(*a*) has also shown that histamin exerts a synergic action when administered just before the reinjection.

On the other hand, there are numerous substances to which has been attributed the property of partially or completely protecting a sensitized animal against the intoxicating dose. Friedberger and Hartoch showed that guinea-pigs may be partially protected by 1 c.c. of a saturated solution of sodium chlorid injected intravenously before the antigen is given. Richet and his collaborators have also protected dogs by intravenous injections of sodium chlorid solutions. Biedl and Kraus, as mentioned above, obtained in dogs a non-specific anti-anaphylaxis by injecting intravenously 0.25 to 0.5 gm. of peptone per kilo of body weight, though Besredka was unable to show that anaphylatoxin had a similar effect in guinea-pigs and one of us has confirmed these results with histamin. Barium chlorid, urethan, chloral hydrate (Auer) and methyl guanidin have all been credited with the property of rendering animals less susceptible to the anaphylactic injection. Ether narcosis was recommended by Besredka as a procedure which lowers the mortality of reinjected guinea-pigs by lessening the irritability of the bronchial musculature. Auer(*a*) found that the intravenous or subcutaneous injection of atropin protects 70 per cent of sensitized guinea-pigs against the minimal lethal dose of antigen. Adrenalin, by sympathetic stimulation relaxes the bronchial musculature and in this way lessens the severity of the anaphylactic reaction in those animals in which bronchial spasm is an important factor. In man, its effect is marked, though fleeting, in anaphylactic reactions characterized by respiratory difficulty and urticaria. Sodium oleate has been found by Kopoczwski and Vakram to suppress the symptoms of guinea-pig anaphylaxis. They attribute its effect to a reduction of plasma surface tension, and found that other substances such as saponin, sodium taurocholat and sodium glycocholat, which also reduce surface tension have a similar prophylactic effect upon animals subjected to reinjection of the antigen.

An interesting type of interference with sensitization has been described by Julian Lewis who found that when comparatively large quantities of a protein different from that employed for sensitization were injected simultaneously with the dose of sensitizing protein, or shortly

afterwards, sensitization was inhibited. This holds both for active and passive sensitization. Thus, dog serum in quantities of 2.00 c.c. to .5 c.c. injected with or shortly after 0.1 c.c. of horse serum in guinea-pigs, prevents active sensitization of the guinea-pig to horse serum. The explanation is similar to that offered by Richet and his co-workers for the preventive action of NaCl for in the one case there is supposed to be a saturation of the cells of the body by NaCl, so as to exclude a union with the anaphylactic poison, and in the other a saturation of the cells of the body with one foreign protein so as to exclude the union with another.

The suggestive observation made by Henrich that treatment of guinea-pigs by the X-Ray suppresses sensitization of the animal to foreign protein has been partially confirmed by Murphy, Hussey and Stearn and Nokahofa.

The Relationship of Experimental Anaphylaxis to Diseases in Man.—It has been quite obvious now for many years that anaphylaxis, as developed experimentally in the animal, has an important bearing in explaining either directly or by analogy a number of pathological conditions and states in the human being. Indeed, interest was first awakened in this subject by the complete studies of von Pirquet and Schick on serum disease. Later, during the development of the experimental investigations upon anaphylaxis, the symptoms presenting themselves in animals suggested to a number of observers analogies to disease states in man, the origin of which had hitherto been very obscure or unknown. It has thus come about that certain cases of asthma, hay-fever, urticaria, angioneurotic edema, acute gastro-intestinal disturbances and idiosyncrasies to certain foods and drugs are considered as manifestations of anaphylaxis in the human being.

It is not our object to discuss in detail evidence which has been brought forward to uphold these views nor to present the clinical features of these common disorders that have been so frequently and so accurately described, nor indeed to present a complete account and analysis of the methods employed in determining the substance to which these patients may be hypersensitive. It is, however, necessary to record to some extent the metabolic disturbances that have been observed under the above conditions in the human being and to compare in a general way, first, the definite disease, serum sickness, and secondly, the more obscure conditions grouped together under the term "idiosyncrasies," with experimental anaphylaxis in animals and with the analogous disturbances brought about by intoxication by poisonous derivatives of protein hydrolysis such as the proteoses and histamin.

Serum disease itself has no definite prototype in the experimental anaphylaxis of animals. The clinical picture in the human being has

not so far been reproduced in the animal. One can add little to the excellent original description by von Pirquet and Schick and that more recently published by Jochmann.

Serum disease may be defined as an abnormal condition produced in man by single or repeated injections of heterologous sera and characterized by the appearance of various types of eruptions, fever, arthralgia, adenopathy, edema and occasionally nausea and vomiting. The incubation period of the disease following the introduction of serum varies somewhat in different individuals and according to whether the individual has had previous injections of the same foreign serum. Depending upon these factors, von Pirquet originally recognized three types of reaction, namely, the normal reaction which occurred from 6–10 days after the first injection of serum, the accelerated reaction appearing 3–5 days after the injection of serum and the immediate reaction appearing within the first 24–48 hours after the injection of serum.

In the normal serum reaction, 6–10 days elapse as a rule between the injection of serum and the first appearance of the outspoken signs of the disease. In most instances, serum sickness starts with swelling of the lymph nodes, and very frequently those nodes which drain the area of the body into which the serum has been injected are the first to enlarge. Within 24–48 hours, the adenopathy becomes general. By this time characteristic rashes occur which appear as urticarial wheals of various sizes, affecting the skin of all parts of the body or as diffuse erythematous and scarlatiniform itching eruptions. Accompanying, or following, the eruption there is very frequently edema of the eyelids, face and ankles, and, in severe cases, actual anasarca. Fever varying from 100° to 102° Fahr. is common. In a small number of cases arthralgia appears, first manifesting itself frequently in the temporomaxillary joint, and, though the joints are not red or swollen except in the rarest instances, they are exquisitely painful, and motion may produce excruciating pain. Some patients complain of pains extending down their arms or down their legs, and in such instances the muscles of the arms and legs may be distinctly tender. In severe cases practically every joint in the body is involved, though the large joints are the ones that are most frequently affected. Usually there is some headache with prostration and malaise during the height of the disease, though this is not often a striking feature. In rare cases nausea and vomiting occur. The spleen is occasionally enlarged and may be palpable. The urine in most cases shows no albumin, even during the period of edema. The blood, during the early stages of the disease, presents a polymorphonuclear leukocytosis, but later it is common to observe a leukopenia with an increase in the lymphocytes. The disease may last only 24 hours or may be protracted over 2–3 weeks. In severe cases there may be relapses at from 7-day to 2-week intervals. According to some observers the relapses

are more frequent when serum containing several protein constituents is employed, and it has been suggested that separate attacks are caused by distinct and individual reactions towards the different protein constituents of the serum. To uphold this view, Dale has shown that the time interval between the injection of serum globulin and serum albumin in animals and the development of sensitiveness of the cornu of the uterus of the sensitized guinea-pig towards the application of the serum globulin and serum albumin differs by an interval of several days.

Recovery is complete, and there are no complications or sequelæ save an altered state of the tissues or hypersensitiveness towards the protein employed which may persist for years.

The development of this state of hypersensitiveness, results, as was shown by von Pirquet and Schick, in a condition of the tissues that explains the immediate and the accelerated reactions following the second dose of heterologous serum from the same animal. Two forms of the immediate reaction were observed. First, the local, when, within fifteen minutes to an hour after the subcutaneous injection of the specific serum, edema, erythema or urticaria appears at the site of the inoculation, and second, the general immediate reaction which is characterized by a more or less severe type of serum sickness coming on within 12–24 hours after the injection of serum.

In the accelerated reaction more or less characteristic serum sickness follows the injection of serum. The incubation period is shorter than that observed after the first injection of serum and lasts but 3–5 days. The frequency with which these secondary types of serum sickness are likely to follow the second injection of serum varies. This is dependent somewhat upon the time interval between the first and second injections for both the accelerated and immediate reactions are more likely to appear when the second injection is made within 1–2 years after the first than when several years have elapsed. There seems, however, to be some variation amongst individuals, and the increased susceptibility undoubtedly persists longer in some individuals than it does in others, so that, occasionally, within a period of 5 or even 8 years, a second injection of specific heterologous serum may call forth either an immediate or an accelerated reaction.

Undoubtedly, profound though temporary changes take place in the tissues of the body during serum disease. Von Pirquet and Schick showed that in children even though a subcutaneous edema was not noticeable there occurred during the serum sickness a relative increase in the weight of the body which was considered as an evidence of the retention of fluids during this period. A more exact analysis of the water and salt exchange in cases of serum disease made by Rackemann, Longcope and Peters showed that, during the period of serum disease, there is a marked but transient retention of chlorids and water, associated sometimes with a

slight albuminuria and cylindruria and occasionally with an impairment of the excretion of phenolsulphonephthalein by the kidneys. In the patients who presented edema with gain in weight during the serum sickness, the plasma chlorids were below normal. There was no noticeable retention of nitrogenous products in the blood of these patients as estimated by the non-protein nitrogen of the blood and by the blood urea. No accurate observations have been made upon the nitrogen balance in the period of serum sickness, and it is, therefore, impossible to determine whether the same loss of nitrogen occurs in the human being during this period as has been described in animals following shock, nor have careful studies been made of the alterations in the serum ferments. Therefore, the field of protein metabolism in this disease is practically unexplored.

The few observations upon the coagulation of the blood would indicate that, even in patients who develop a purpuric eruption during the course of serum disease, the normal factors concerned in the coagulation of the blood are not disturbed. The resistance of the capillaries of the skin to injury or increased intravascular tension, however, may be diminished in patients who develop purpura during the course of the illness.

Much discussion has arisen as to the exact mechanism by which serum disease is brought about. As was originally shown by von Pirquet and Schick, and has been demonstrated by Hamburger and Moro, Weil, C. Wells, and Francione, specific precipitins for horse serum occur in the circulating blood of the patient during or following the serum illness. It was at first believed that the appearance in the circulation of these precipitins and their subsequent union with the antigen in this situation were responsible for the disease, but later observations have not upheld this view and the observations of Longcope and Rackemann, Weil, and Mackenzie and Leake would indicate that the appearance of circulating precipitins as well as other antibodies such as the anaphylactic antibody are the result rather than the cause of serum disease and act in the capacity of a protective mechanism to rid the body of antigen and thus bring about a spontaneous cure of the disease. It has further been shown by Mackenzie and Leake, that in the small group of patients who are insusceptible to serum disease, even when large amounts of foreign serum are given, that these antibodies are not demonstrable in the circulating blood, or appear in slight concentration and that the antigen or horse serum continues to circulate as an innocuous substance for weeks or months. They suggest that the person susceptible to serum disease possesses some mechanism which prevents the union of antigen (horse serum) with the body cells, but the exact explanation of this mechanism is as yet lacking.

Though many factors concerning the development and the recovery from serum sickness are still very obscure, the study of this disease has been aided by the fact that fairly well defined, though complicated protein substances have been introduced in known quantities into the cir-

culation or tissues of the normal human being and the problem has presented many of the features and opportunities that occur with any experimental investigation. It has been possible, therefore, to deal with factors some of which are known and part of which can be controlled. Even under these circumstances great obscurity still involves the underlying processes of the disease and it is no wonder, therefore, that the still more complicated and difficult subject of hypersensitiveness or idiosyncrasy in which factors cannot be controlled should, in spite of much investigation and study, present considerable mystery.

It has been known for many years that certain individuals respond in an abnormal manner to substances that are quite harmless to the ordinary person. This peculiar idiosyncrasy may be manifest after the inhalation, ingestion, or the skin contact with the substance in question. Such idiosyncrasy or forms of hypersensitiveness have been shown to occur in a certain proportion of individuals suffering from a variety of diseased conditions such as hay fever, asthma, acute gastro-intestinal disturbances, particularly in children, and such affections of the skin as urticaria, eczema and angioneurotic edema. It has further been demonstrated that the inhalation, the ingestion, or the skin contact with one of several proteins or even of substances that are non-antigenic in nature, may precipitate an attack of the disease from which the patient may be a chronic sufferer. Thus inhalation of ragweed pollen may precipitate an attack of hay fever, or the inhalation of the epidermal dust of horses, dogs, and cats or of fowls, may produce severe attacks of asthma in one hypersensitive to any one of these proteins; while the taking of an egg or of cow's milk, of certain fruits or vegetables, of quinin or the salicylates, may always call forth in a given individual an attack of urticaria, asthma, or of violent nausea and vomiting. And finally, the cutaneous contact with the pollen of ragweed or the juice of a nasturtium or the leaves and pollen of primroses may constantly give rise to urticaria or dermatitis in one who has an idiosyncrasy for these substances.

A comparison of the condition which exists in those individuals who present such idiosyncrasies with that brought about by artificial sensitization of the guinea-pig or rabbit, or with the hypersusceptibility or allergy developing in the human being after the injection of foreign proteins such as horse serum, discloses on the one hand important analogies and on the other brings out differences so that at the present time it seems desirable to consider this state of hypersensitiveness as a condition requiring study for its own sake and not because of the similarities which it presents to experimental anaphylaxis.

The similarities indeed depend largely upon the train of symptoms caused by the intoxication following the contact with the specific substance to which the person is idiosyncratic and these symptoms may vary from a mild rhinitis or localized urticaria to a violent condition of shock, with

acute suffocation, asthma, terrific engorgement of the tissues of the neck and chest with collapse and death. The latter picture is rare unless the offending substance is introduced subcutaneously or intravenously, and though very alarming symptoms have followed the taking by mouth of proteins to which the patient is hypersensitive, death rarely, if ever, occurs under these latter conditions.

The etiology of this condition is still very obscure. At first sight and in accordance with the experience obtained from experiments upon the guinea-pig, it might seem to follow naturally that the mere parenteral introduction of any foreign native protein in the normal individual would be sufficient to explain the development of these extraordinary idiosyncrasies. It is highly probable indeed that foreign native proteins often gain access to the body tissues either through artificial means, the method which certainly occurs in therapeutic inoculations of foreign serum, or by natural methods. It has, for instance, been shown by Schloss and Worthen(*a*) and by Grules and Bonar that a fair proportion of infants absorb egg albumen from the gastro-intestinal tract and excrete this protein unchanged in the urine. Apparently the absorption of this protein unchanged is much more likely to take place during acute and chronic gastro-intestinal disturbances than under normal conditions, but Grulee and Bonar have recently shown that many normal infants, free from gastro-intestinal disturbances, may absorb and excrete egg albumen up to the 11th day of life.

But it is obvious that only small quantities of foreign proteins could come in contact directly with the tissues or the fluids of the body by this method, and since it is known that man is much less readily sensitized than many of the lower animals such as the guinea-pig, it does not seem likely that the absorption of foreign native proteins through the mucous membranes of the gastro-intestinal tract or of the respiratory tract, or through the skin can account alone for the exquisite sensitization which is often observed in the human being. Even in the animals such as the guinea-pig that lend themselves most readily to experimental sensitization, the process is accomplished with much more difficulty when the foreign protein is applied to the mucous membranes than when it is injected beneath the skin or into the peritoneal cavity or intravenously.

Indeed, such a mechanism could not account for the exquisite hypersensitiveness of the child who reacts by a violent attack of vomiting or urticaria upon the first occasion when he is given egg by mouth, or for the fact that the skin of certain individuals may show an extraordinary idiosyncrasy towards a substance with which they could not previously have come in contact. In many cases a third and important factor must be taken into consideration, namely, the familial tendency towards idiosyncrasies. It has been established that these idiosyncrasies may occur very definitely in families and Cook and Vandeveer have brought out the fact

that hay fever affects members of families in a proportion which closely approximates the theoretical figures of the Mendelian law and suggests that idiosyncrasies may be inherited as a dominant characteristic. Other observers who have studied this aspect of the question are of much the same opinion and it seems fairly well established now that a condition of the tissues, at least, may be inherited that renders the individual highly prone to the development of hypersensitiveness. The idiosyncrasies themselves may differ in the different members of the same family and may assume quite different forms of expression. Occasionally, all members of the family may have hay fever, but in some, it may be caused by ragweed and in others by timothy. On the other hand, one member may have hay fever, another horse asthma, and a third egg eczema and urticaria.

A comparison of the degree of hypersensitiveness which is present in these individuals with that produced artificially by the injection of serum in human beings, or with that obtained experimentally in animals, shows that it is much greater in the former group. Thus, severe or even alarming symptoms may be produced in an asthmatic who is sensitive to the pollen of ragweed or to the epidermal dust of horses, by the subcutaneous injections of such minute quantities as 0.1 c.c. of 1-500 or even 1-10,000 dilutions of an extract prepared from ragweed pollen or from the hair and epidermal scales of a horse. And in the same individual, an intracutaneous injection of a drop of 1-1,000 or even 1-100,000 dilutions of these extracts may call forth an intense local reaction with the formation of an urticarial wheal 2–3 cm. in diameter, surrounded by a zone of erythema 5–8 cm. across. Such responses are almost unknown, either in the artificially sensitized animal or human being, and indicate a degree of reaction in the tissues or body fluids of these hypersensitive individuals which have so far been unobtainable experimentally.

Observations have shown that in the hypersensitive individual, the reaction may be called forth by the introduction of minute quantities of the material, either to a scarified area of the skin (the cutaneous test), by injection of minute quantities of high dilutions of the protein into the superficial layer of the skin (intradermal test) or by local applications to the mucous membrane of the nose or the conjunctiva. It has been further determined that the degree of reactivity of these tissues may vary to the same protein, in different individuals who are known to be hypersensitive to the same protein substances. Those who show the greatest degree of sensitiveness react perhaps violently to the protein when tested by all methods, those showing a lesser degree of sensitiveness may fail to react when the material is applied to the scarified skin, but respond in a characteristic way when the protein is placed upon the mucous membranes or injected into the skin; while finally the slightly sensitive individual reacts solely to the intradermal test. As a rule the local reactions appear within 15–30 minutes after the application is made, and

are comparable to the immediate reactions described by von Pirquet. Occasionally delayed reactions are observed in which the urticarial wheal and erythema make their appearance, only after an interval or latent period of from 2–4 to 12–24 hours after the test is performed.

Not only are there variations in the degree of hypersensitiveness to the same proteins in different individuals, but in a single individual the different tissues may vary so absolutely in their sensitiveness to the same protein that the impression is obtained that the sensitiveness is highly developed in some tissues and entirely absent in others (local hypersensitiveness). Occasionally, instances are recorded in which an extract of pollen or of some protein calls forth no reaction when the dermal or intradermal test is employed, but produces a very marked reaction when applied to the mucous membrane of the nose or conjunctiva. In other individuals, the application of the protein or an extract to the skin may result in a violent reaction, whereas ingestion of the protein and contact with the mucous membrane of the mouth and gastrointestinal tract produce no observable effect.

Some observations have recently been made by Mackenzie and Baldwin to show that these local reactions are in all probability true cellular reactions and represent a union of the antigen with the cells with which it comes in contact. They have found that the repeated application of a protein such as egg white or an extract of ragweed to a single area of the skin of an individual hypersensitive to either one of these substances results in a gradual diminution of the local reaction until finally, after several applications, there comes a complete exhaust in the localized area of the skin, so that it no longer shows any reaction to the application of these substances. This exhaustion of reactivity of the tissues may persist for 3–5 days, and then gradually return. The exhaust appears to be specific. The exhaustion of the reactivity of the tissues to the specific protein is not interfered with by the application of histamin, a non-specific toxic amin which causes an urticarial wheal when applied to the skin, nor does it interfere with the reactivity of the tissues towards histamin. The local, rapid, and specific exhaustion of the tissue to the application of a substance to which the individual is hypersensitive probably explains the beneficial results which have been obtained both by the feeding of egg white in gradually increasing doses to children who are susceptible to egg white, as well as the prevention of hay fever and asthma by the subcutaneous injection of gradually increasing amounts of the extract of pollens or other substances to which these individuals may be hypersensitive.

It may thus be seen that considerable variations occur both in the degree of hypersensitiveness of different individuals and of the participation of different mucous and cutaneous surfaces as regards the hypersensitiveness to a given protein in the same individual.

Another characteristic of the individual who shows these idiosyncrasies is that his tissues are likely to react to more than one substance, and as a rule about one-half of the patients show what has been termed multiple sensitization. The variety of material which calls forth these reactions and are known to produce the symptoms in many of these hypersensitive individuals, is very great and is not confined to the proteins or those substances producing antibodies when injected into animals. Not only are reactions obtained to the extracts of many pollens of plants, such as ragweed and timothy in the hay fever patients, extracts of hair and the epidermis of both domestic and wild animals and fowls in the asthmatics, preparations of blood serum from these same animals or extracts of their meat, or of fish, vegetables, nuts and various fruits, as well as preparations of egg albumen, of milk and of cereals, which are often responsible for the eczemas, especially in children; but symptoms may also be produced and skin reactions obtained from the use of a variety of crystalloids and of drugs and chemicals. Since these latter substances contain no protein, as far as one can determine, it is difficult to explain their action upon the same hypothesis as that used to elucidate the anaphylactic reaction in animals. Of the crystalloids, White has described cutaneous reactions to lactose in eczematous children. The metals and drugs which have been reported as producing symptoms and which are responsible for the idiosyncrasies cover a wide field and include the true metals (mercury and arsenic); the halogens (iodin); the alkaloids (quinin); the methane derivatives (iodoform); cold tar products such as antipyrin, benzol derivatives and others.

Attempts have been made to correlate these reactions from drugs with those produced by protein substances, by assuming that the drug or metal united with the protein of the individual to form a new protein substance and evidence has been brought forward by Friedberger and Ito(*a*), to show that guinea-pigs may be sensitized to a mixture of iodin and guinea-pig serum or to a mixture of salvarsan and a guinea-pig serum. It is perhaps possible to conceive that in the drug and metal idiosyncrasies, such a combination does take place between the blood serum of the individual and the drug or metal, and that thus a new protein is formed. So far, however, there is no evidence in human beings which would confirm this hypothesis. It is true that some of these drug idiosyncrasies do develop only after repeated use of the substances. This has been the case with salvarsan and arsphenamin idiosyncrasy, that developing after the repeated use of atoxyl and that recently described by Gerden which develops in dye workers and is caused by the inhalation of p-phenyldiamin or ursol. In the latter instance, the dye is used for coloring fur and one might be suspicious that the sensitization had been produced towards the epidermal dust of the animal skins rather than towards the dye. Though perhaps gradual sensitization after repeated use is common in drug idio-

syncrasies, spontaneous hypersensitiveness does occur and symptoms may appear after the first use of the drug.

Though multiple sensitizations are common in the idiosyncrasies and occur in approximately 50 per cent, the groups of substances to which the patients are sensitive are not always of one type, and though certain individuals may react to several varieties of plant pollen and others to the proteins of eggs or to the extract of vegetables only, this is by no means uniform, and frequently individuals are encountered who may react not only to pollens but to the extract of animal dust and to egg albumen. Also in spite of these multiple reactions, there seems often to be a specific selection amongst the different proteins which go to make up a complex substance such as egg white, cereal seeds or animal hairs. The patient may show a typical reaction with ovomucin, but none to ovalbumin; a typical reaction to wheat proteose, but none to wheat gliadin or leucosin; to horse dander, but not to horse serum or to the alkali metoprotein of dog hair, but none to the peptone or vice versa.

It is difficult, therefore, to understand this multiple sensitization on the basis of a group reaction or upon the basis of non-specific sensitization.

It is interesting too to note that the presence of circulating antibodies in these naturally hypersensitive individuals is extremely rare and though isolated reports of specific precipitins, of complement fixing antibodies and of passive transfer of sensitiveness to guinea-pigs with the serum of individuals who showed idiosyncrasy to such varied proteins, as pollen, egg white and the extract of horse dander have been recorded, most observers have failed consistently to obtain such results.

One instance has been reported by Ramirez of possible transfer of hypersensitiveness to horse dander by transfusion of blood from one human being to another and if this, by accident, should be repeated, it would have important bearing on this entire subject.

To summarize this part of the subject, one may say that the natural idiosyncrasies or allergies which occur towards various proteins and even non-protein substances, such as drugs, differ in such essential respects from the true experimental anaphylaxis in the animal and indeed from the artificial sensitization in man, the prototype of which is serum disease, that one cannot at the present time consider this group of individuals who are so frequently sufferers from hay fever, asthma, eczema, urticaria, etc., in the same category as the animal who has been sensitized to a foreign protein. Some investigators and notably Coca take rather the extreme view and consider that all these manifestations in the human being are to be considered as instances of allergy and as different fundamentally from anaphylaxis. Coca would include in this category not only the spontaneous sensitization, both to protein substances and to such chemicals as drugs, but artificial sensitization in the human being as well as serum

disease. The facts, however, do not appear to warrant such a sweeping conclusion and it would seem more in accordance with experimental evidence to consider serum disease and the various results of the artificial introduction of native proteins parenterally into the human being as following the same principles that govern the reactions in the anaphylactic animal. This was the conception which was originally held by von Pirquet and Schick and which has been emphasized by Longcope and Rackemann and by Mackenzie and Leake.

When one considers the relative susceptibility of different species to sensitization by foreign proteins, it is found that this varies considerably. The guinea-pig represents the animal which is most susceptible to sensitization by foreign proteins. The dog and the cat come somewhat lower in the scale and it is well known that it is considerably more difficult to sensitize the rabbit than perhaps any of these animals. Previously, it was thought that the lower monkeys could not be made anaphylactic towards horse serum but recently it has been shown by Zinsser that the Macacus rhesus and the Cebus monkey may be made anaphylactic, both to horse serum and to egg white, though sensitization is attained with some difficulty and, as indicated by tests made with the Dale method, of uterine muscle strips, is only of moderate intensity. The susceptibility to artificial sensitization places the human being in this scale apparently above the monkey.

It seems desirable, therefore, to consider serum disease and the effect that follows artificial sensitization in man as analogous to anaphylaxis in the experimental animal and to separate into a second class the spontaneously or naturally hypersensitive individuals, the relation of which to experimental anaphylaxis is not clear and the fundamental principles of which need considerable investigation and study irrespective of the relationship of this condition to experimental anaphylaxis.

Though the diseases associated with spontaneous sensitization such as hay fever, asthma, eczema, urticaria and the acute gastro-intestinal disturbances of both infants and adults, have of themselves been familiar for many years and though great numbers of these patients now have been subjected to skin tests, to determine whether or not they belong to the group of spontaneously hypersensitive individuals and whether or not the materials to which their skin shows hypersensitiveness is responsible for their symptoms, it is surprising how comparatively few investigations have been made upon the physiological and chemical reactions of this group of patients who are proven to show such idiosyncrasies. Examination of the blood has shown that in asthma there is quite frequently an increase in the eosinophilic leukocytes, but this is by no means a regular finding in the case of individuals with spontaneous hypersensitiveness and perhaps a more constant and a striking feature of this dyscrasia in adults is the relative increase in the small lymphocytes of the blood.

Observations dealing with the metabolism of these patients are most striking by their absence. It is a perfectly familiar observation that patients with asthma or urticaria are prone to lose weight and that when their symptoms cease, they rapidly increase in weight. Exactly what this loss of weight is due to, however, is not known and there are so many factors, such as improper feeding or even the abstinence from food by the patient, loss of sleep and constant anxiety or distress which many of these patients suffer, that it is impossible to determine what factor is responsible or how important the various factors are in bringing about this frequent loss in weight.

In a few cases of urticaria, known to occur in naturally hypersensitive individuals, the chemistry of the blood and the function of the kidneys have been studied before and during attacks. Thus, in six cases of urticaria which were made a subject of study by Longcope and Rackemann, it was found that two showed very marked temporary renal insufficiency during the attack of urticaria. In one patient, who was sensitive to beef and sheep protein, the attack of urticaria was associated with a rise in blood urea, a decrease in the phthalein output, suppression of urine and almost complete suppression of chlorid and nitrogen excretion. During the period immediately after recovery, the nitrogen excretion and chlorid excretion were excessive, when the blood urea, the phthalein output and the water exchange returned to normal. During this same period, there was a loss of almost eight pounds in weight. The second case which was not shown to be hypersensitive to any of the proteins with which tests were made, belongs perhaps more properly in another group which will be discussed in a later section. It must be admitted, however, that there is almost complete lack of information and of study concerning the finer chemical and metabolic changes which take place during the crises of intoxication in these naturally hypersensitive individuals, and there is further no definite evidence that such crises result in any permanent injury to the organism.

Despite the fact that in the literature there are numerous reports upon the alteration in metabolism caused by dyspnoea, little attention has been paid to the metabolism of patients with bronchial asthma either in the interval between the attacks or during the paroxysm. Zugsmith and Kahn(*a*) studied the nitrogen partition and the mineral excretion in the urine of two patients with bronchial asthma. Presumably the studies were carried out in the intervals between attacks, although it is not so stated in their paper. The findings seem to agree very well with the results obtained in experimental animals. Apparently there is a condition of tissue suboxidation which results in an increase in the non-oxidized "neutral" sulphur and a lowered excretion of creatinin. Since the amount of the latter in the urine is dependent only on endogenous katabolism it

seems probable that its diminution in asthma results from lessened tissue oxidation.

As regards the effect of extraneous disturbances in precipitating symptoms in these individuals, it is necessary to refer again to the work of Auer who showed that in the rabbit, sensitized to horse serum and later reinjected with horse serum, a marked local inflammatory reaction occurred at a point of chemical injury such as that produced in the ear by zylol. He explains this reaction by assuming that antigen reaches the injured ear, escapes into the tissue and for this reason produces a local reaction which would, without the previous chemical inflammation, be impossible. This work is most suggestive, inasmuch as it furnishes some experimental basis for suspecting that local non-specific injury to such tissues as the skin and mucous membranes in hypersensitive individuals may in the presence of specific antigen bring about a condition which allows a violent reaction to take place.

Protein Intoxication.—A closely related phase of this entire subject, namely, the effect produced in the animal and in man by the absorption or the injection of protein split products that are in themselves highly toxic, has already been referred to in the discussion relating to the etiology of anaphylaxis. The toxicity of these products of protein disintegration has been known for many years, for, as long ago as 1880, Schmidt-Mulheim and Fano pointed out that the intravenous injection of proteose-peptone into animals caused profound disturbances of shock-like character. For many years following these observations, the toxic action of such substances was studied and described, but the subject assumed a position of new importance when Biedl and Kraus called attention to the striking resemblance to anaphylactic shock of symptoms produced in dogs by the injection of peptone solution. Since then, poisonous substances have been obtained by a great variety of methods from protein and it has been shown that these substances or changed proteins are toxic for animals and when injected result in symptoms that are in general similar and in many animals resemble anaphylactic shock. Much impetus was given to such studies by the investigations of Vaughan upon the protein poisons obtained from bacteria. The hypothesis that toxic split proteins were responsible for anaphylactic shock was supported by Friedberger, who described the production of a toxic substance by the action *in vitro* of antigen, antibody and complement, which he termed anaphylatoxin. Still another phase of this subject is represented by the work of Jobling and Peterson, who, by extracting the lipoid from blood serum or by treating blood serum with potassium iodid, demonstrated that it became toxic. In their opinion and in that of Bronfenbrenner this process removes all anti-enzymes and allows of the cleavage of the proteins of the serum by its own proteolytic ferments. That blood serum may develop somewhat the same

form of toxicity towards animals has been shown by Novy and De Kruif, through purely physical processes and even by the mere coagulation of shed blood. That toxic substances may be formed in blood serum by a great variety of methods has indeed been amply demonstrated and already referred to, but the exact explanation of the evolution of the inert serum into a toxic one, and the toxic chemical substance, if there is one, which is produced under these varying circumstances is as yet imperfectly understood.

It seems highly probable that whatever the method employed, the toxic substance is derived from the serum itself, but whether by the action of specific ferments, an explanation that seems unnecessary, or by non-specific enzymes or through purely physico-chemical means is not definitely known. That proteins may be split through hydrolysis to the amins, many of which are toxic, has long been recognized but the identification of many of these toxic amins and their importance as a constituent of the proteins of higher molecular form, is in part a matter of conjecture.

This whole subject has recently been discussed by Koessler who states "that from the point of view of chemical composition, these amins may be divided into two classes. The mono-amins, like isobutylamin, isoamylamin phenylethylamin, p-hydroxphenylethylamin and indolethylamin, which have one basic N group; and the diamins, as tetramethylin diamin and pentamethylin diamin (petruscin and cadaverin), agmatin, the amin derived from arginin, and imidazolethylamin, which have two basic N groups. This difference in the chemical composition of each group is associated with a corresponding diversity of physiologic action. The most active compounds are those that have a ring structure with a side chain of two carbon atoms. As representative of the mono-amins, p-hydroxphenylethylamin will serve as an example. The substance tyramin, which belongs to the first or mono-amins, has received considerable experimental study, but for various reasons much more work has been devoted to a study of the diamins which contain two nitrogen groups. To this group belong indolethylamin, putrescin, and cadaverin; agmatin, the amin derived from argenin and imidazolethylamin or histamin, the base derived from the amino acid histidin." It is to the latter substance, particularly, that extensive study has been devoted in recent years; and the results of the experiments of Barger and Dale(*a*), of Dale and Laidlaw(*a*)(*b*), Dale and Richards, and of Abel and Kubato have increased our knowledge extensively concerning the pharmacological and toxic action of this substance. The similarity between the toxic effects obtained by this chemical and those observed in anaphylactic shock have been extensively discussed by Dale and already have been referred to, and it is only necessary to emphasize the fact that this substance affects very markedly the smooth muscle of the animal and acts furthermore as a capillary poison. Abel and Kubato

concluded from their work that the distribution of histamin was very wide and that the toxic action of peptone and of the proteoses as well as some of the effects obtained from the injection of the pituitary body are dependent upon histamin. Koessler, however, has shown that though histamin occurs in Witte's peptone, it is not responsible entirely for the toxic action of Witte's peptone.

The extremely toxic action of many of these diamins and their derivation from proteins on the one hand and the readiness with which toxic substances may be formed in blood serum *in vitro* on the other, has naturally led to the suggestion that under certain conditions, such poisons may be formed in the human body and be responsible for acute intoxications or chronic illnesses.

It has been shown, for instance, that histidin which occurs in the final splitting of protein may, by the action of bacteria, be partially converted into histamin. But at the present moment there is little direct evidence to indicate that such substances occur in pathological states in the human being or are responsible for any definite group of symptoms. One of the intoxications that has been written of and talked of for many years is the so-called ptomain poisoning, and it has now been shown that spoiled foods, which have caused widespread intoxication, may contain substances that give reactions similar to some of the diamins. Thus, Blankenhorn, Harmon, and Hanzlik have described the poisoning of a group of persons by canned codfish, which they believed was not due to bacterial contamination of this food, but dependent upon a chemical substance that they could obtain from the salted codfish and which gave pharmacological reactions that made them feel that it was probably histamin.

The experiments of Whipple, Stone, Bernheim, Rodenbaugh, Cook, and McQuarrie upon experimental intestinal obstruction in dogs seem to show that under these conditions there is formed a poison particularly in the upper intestinal tract which they identify as a proteose and which produces, upon injection into normal animals, a condition simulating the shock following experimental high intestinal obstruction. One of the characteristics of this proteose intoxication in animals is a sudden increase of the non-protein nitrogen of the blood together with a decrease in the phthalein excretion in the urine. This is not associated with anatomical lesions in the kidney and may result from the injection of the proteose substance obtained from the intestinal loops of dogs subjected to experimental intestinal obstruction. In man, many of the symptoms of high intestinal obstruction are much the same as those observed in the artificial obstruction produced in animals, and Tileston and Comfort first noted in cases of acute intestinal obstruction, that the non-protein nitrogen of the blood might be elevated to as much as 150 mgm. to 169 mgm. per 100 c.c. With the relief of the obstruction in two cases that recovered, the non-protein nitrogen of the blood returned to normal. One similar

case has been reported by Cook, Rodenbaugh and Whipple. Recently, Louria has described cases of intestinal obstruction from the Presbyterian Hospital, and has shown that during the period of acute obstruction, the blood urea may be markedly elevated. In those cases that recover, the blood urea returns to normal. In fatal cases, the kidneys have shown no abnormalities which could be interpreted as nephritis. In one of Louria's cases there developed a generalized urticaria and erythema.

It is highly probable that other forms of intoxication may arise from the absorption of toxins formed in the gastro-intestinal tract, during which there may be such profound disturbances in the protein metabolism of the body that the non-protein nitrogen constituents of the serum are temporarily increased and the function of the kidney temporarily interfered with. Such an instance occurred in one of a group of cases reported by Longcope and Rackemann, wherein a violent attack of diarrhea in a woman fifty-eight years old, was followed in five days by an elevation of the blood urea to 295 mgm. per 100 c.c. On the 11th day after the onset of the diarrhea, there developed a profuse and generalized urticaria and erythema which persisted for 6 days and was accompanied by a leukocytosis of 44,600 with 76 per cent polymorphonuclear leukocytes. With the disappearance of the eruptions the blood urea fell to normal, 22 mgm. per 100 c.c. The leukocyte count dropped to 8,000 but the eosinophiles increased proportionately to form 23 per cent of the granular cells. The substances which may produce these forms of intoxication in the human being are as yet unidentified, but from the few careful observations that are on record, they seem to be associated with a marked disturbance in the general protein metabolism and by the accumulation in the blood serum of abnormal quantities of non-protein nitrogen. They are likewise accompanied at times by urticarial or erythematous eruptions which do not differ essentially from those observed in cases of serum disease. Similar changes have been observed by Schloss in the blood of infants suffering with intestinal toxemia. In a series of 46 such cases, he found in 33 an increase in the blood non-protein nitrogen from 57 to 232 mgm. per 100 c.c. and of the blood urea nitrogen from 20.1 to 108 mg. per 100 c.c. The condition was accompanied by a lowering of the blood CO_2 which is not due to the formation of ketone bodies but retention of phosphates as was shown by Marriot and Howland and is associated with great loss of water from the body. The excretion of water was diminished to almost nil, and though there was no evidence of actual disease of the kidneys, Schloss concludes that the retention of nitrogenous products is dependent upon faulty elimination resulting from the small fluid output.

Aside from these intoxications, which are associated with disturbances in the gastro-intestinal tract and which may be dependent upon the formation and the absorption of some toxic chemical derived from protein, a supposition, no matter how suggestive yet purely speculative, there are

more definite evidences that the introduction of protein substances of a complex nature into the human being may be followed almost immediately by a fairly definite train of symptoms. What information we have concerning this side of the problem comes almost exclusively from observations made upon the deleterious effects of the intravenous injection of fluids in man. Aside from the effects produced by hemolysis, other manifestations have been observed which cannot be ascribed to this cause. These effects first received widespread attention when salvarsan came to be administered generally by the intravenous route and when blood transfusions became popular. Previously, it had been noted that occasionally an intravenous infusion of normal salt solution in children was followed by a febrile reaction which was termed in the older literature salt fever. Shortly after the general intravenous use of salvarsan, a similar febrile reaction was frequently observed to follow immediately upon the administration of this drug. This chill and fever appearing either in one or two hours after the administration of salvarsan was frequently accompanied by headache, nausea, vomiting and pains in the back and extremities. The similarity of salt fever and these reactions was frequently commented upon and it was finally shown by Wechselmann that most of these reactions could be obviated by using freshly distilled sterile water for the preparation of the salt solution or of salvarsan. He furthermore demonstrated that distilled water which had stood for any length of time frequently contained a growth of molds and ascribed the untoward reactions to traces of a toxic substance, thought in all probability to be some form of split protein, resulting from the growth or destruction of the molds in this old distilled water. Since the general use of freshly distilled water for the preparations of salvarsan and arsphenamin, the frequency of these reactions (which came to be termed protein reactions) has been greatly diminished. But that reactions may still occur after the intravenous use of arsphenamin is still evident from a recent paper by Strickler, Munson, Sidlick and Strauss. They show that fever, chills, nausea, vomiting, diarrhea, pain in back and extremities may occur in 67 per cent of cases and moreover are as common after the intravenous injection of arsphenamin in normal persons as they are in syphilitics. They are inclined to believe that these reactions are caused by the drug itself.

A somewhat similar type of reaction that has been frequently observed and extensively written about is that following the transfusion of blood. The typical transfusion reaction comes on about one half hour after the transfusion, and is accompanied by a sharp rise in temperature gradually subsiding to normal in from three to eight hours; sometimes nausea, vomiting, pains in various parts of the body and skin eruptions such as urticaria and localized areas of edema. These reactions may vary considerably in degree, the mildest being ushered in by a slight rise of temperature without other symptoms, while in the more severe, the temperature may rise to

as high as 105° and be accompanied by any or all the above symptoms. The occurrence of these reactions is quite common and in a series of 280 transfusions described by Meleney, Stearns, Fortuine and Ferry they were present in 63.6 per cent, varying in degree, but always being evidenced by a rise of temperature to 100° or more. In this series, the method of transfusion, blood relationship of donor and recipient, and the blood group of the recipient seemed to have nothing to do with the occurrence of the reaction. It seemed that reactions were more common after large transfusions and that the blood of some donors was more likely to cause reaction than the blood of others. In some cases the post-transfusion reaction was accompanied by marked polymorphonuclear leukocytosis. These in general are the findings of most observers who have studied post-transfusion reactions and by many it has been thought that these reactions depend upon the formation of some toxic material from the partial splitting of protein, though there is no direct evidence to demonstrate the truth of this conclusion.

Since the investigation upon salt fever, salvarsan reactions and the blood transfusion reactions, somewhat similar reactions have become familiar after the injection of many materials both rich in protein and poor in this substance. Similar immediate reactions are not uncommon after the administration of large doses of serum such as that employed in the treatment of pneumonia due to pneumococcus Group I, while reactions accompanying intravenous administration of bacterial vaccine, milk and other forms of protein, for therapeutic purposes are now thoroughly familiar. This intravenous vaccine or so-called protein non-specific therapy, employed first by Ishikawa and Gay in the specific treatment of typhoid fever with typhoid vaccines, and later by Nolf, Miller and Lusk(*a*)(*d*)(*e*), and Cowie and Calhoun and others in the treatment of arthritis of various forms, is regularly followed by a marked reaction very similar to that already described but particularly noteworthy for the rapid rise and subsequent fall in temperature. As has been shown by Cowie and Calhoun and further by Gow the reaction is characterized by a marked change in the total number of leukocytes; this consists first, in a leukopenia followed by a more or less pronounced polymorphonuclear leukocytosis. There are, however, many features of these reactions which are very imperfectly understood, and, except that they are associated with the injection of foreign protein in some form, we are at present ignorant as to the exact substance which brings them about. In many respects they resemble the reactions brought about in guinea-pigs by the injection into the veins of such substances as kaolin, agar-agar, etc.

There are finally a few observations upon the effect of at least one toxic diamin, namely, histamin in man. It was shown in 1913 by Eppinger and Guttmann that histamin when rubbed into the skin of the normal individual produces an urticarial wheal. A more recent study of

the skin reactions brought about by the amins has been made by Sollmann and by Sollmann and Pilcher, who have shown that though numerous chemicals may produce urticarial reactions in the skin, there are two, namely, phenylethylamin and histamin, which produce the most definite and pronounced response. These observations upon the skin reactions of histamin have now been repeatedly confirmed and are well known. There is one report by Sieburg in which histamin was injected subcutaneously into a woman and was followed almost immediately by generalized urticarial eruptions.

It may thus be seen that very few observations are on record which serve to throw any light upon these so-called protein reactions in the human being and though it is obvious that the introduction, particularly into the circulation, of foreign proteins of many sorts will call forth a very marked and rapid reaction on the part of the body, yet the toxic substance which is responsible for this is unknown, and the question of its origin from the foreign material injected or from the proteins of the individual is as yet unanswered.

Disturbances of Growth . . . . . *E. V. McCollum*

Growth and Chemical Laws—Requirements of Growth—Food Elements and Growth—Vitamins and Growth—Laws of Growth—Optimum Cell Environment—Dietary Factors and Growth—Animal Experimentation.

Disturbances of Growth

E. V. McCOLLUM

BALTIMORE

Our knowledge of nutritional processes is the fruit of human experience clarified by scientific inquiry through experiments on animals. Growth is governed entirely by chemical laws. It represents changes which take place in a heterogeneous system consisting of water, proteins, lipins, inorganic salts, glucose, and at least a few other substances whose natures and functions are not understood. These are arranged in such a manner that they form a system which is self-perpetuating, and capable of increasing its mass at the expense of non-living matter which serves as food. It can repair, through the agency of food, the fractions of its structures which are degraded through metabolic processes. These changes involve the liberation of the potential energy of the foodstuffs. The kinetic energy may appear in the form of mechanical work, heat, light or electricity. It is the increase in mass, accompanied by certain specialization of parts, and a progressive modification of structure and change of form, that constitutes growth.

Every living body and every anatomic unit of living matter requires water, oxygen, certain inorganic elements in the form of appropriate salts, a certain atmospheric pressure, and food. A discussion of disturbances of growth involves a consideration of the effects of improperly constituted food upon the body structures. An understanding of the chemistry of foods is essential to a satisfactory comprehension of nutrition. Unfortunately our knowledge in this field is still far from complete, but methods of study have been devised which have thrown much new light on certain aspects of the subject.

Food, to be complete for the nutrition of a mammal, must supply proteins of a character to furnish the seventeen or eighteen amino acids which are essential for the construction of body proteins. It must contain satisfactory amounts of nine inorganic elements in appropriate combinations. These are calcium, magnesium, sodium, potassium, chlorin, phosphorus, iodin, iron and sulphur. All of these except sulphur can be utilized in the form of inorganic salts such as chlorids, phosphates, etc., of the bases. Sulphur must be furnished in the form of the sulphur-containing amino acid cystin. In addition to these, the food must furnish the

sugar glucose in abundance, for this is the sugar which the cells make direct use of as a source of energy. Furthermore, it must contain sufficient amounts of at least three, and in the case of some species, probably four substances, the chemical natures of which we know nothing. We recognize these dietary factors solely by observing the pathological changes which result from the absence of one or another of them from the diet. These substances have been most frequently designated, "vitamines," following the suggestion of Funk. Since it is necessary to specify which one is meant in any discussion of a specific nature, it has become the practice to speak of them in algebraic terms as fat-soluble A, water-soluble B and water-soluble C, which designate the substance which protects specifically against a type of ophthalmia, beri-beri and scurvy respectively. The fourth substance in this class, whose existence was suggested above, has not been conclusively shown to be distinct from the first, or fat-soluble A, although there is much evidence that it is. It is the organic factor which is concerned with the development and functioning of the osteoblast, and is therefore intimately concerned with the etiology of rickets.

The cells of living tissue have a remarkable power to synthesize many complex organic compounds from relatively simple ones. Notable examples of this power are seen in the capacity of the body to synthesize lecithin, cephalin and nucleic acid during growth, and the phosphorized protein, casein, during milk formation, deriving for all these the necessary phosphorus from the salts of orthophosphoric acid. All of these are compounds too complex for synthesis by chemical procedure in the laboratory. Although the tissues are remarkably efficient in the synthesis of certain very complex organic compounds, they are powerless to affect many others, even of a simpler nature, for their own preservation. Among those which cannot originate by synthesis through the agency of the living cells are the unidentified dietary factors which are concerned with the etiology of the so-called "deficiency" diseases. This last statement needs qualification to a certain extent. It has been shown that the rat cannot be made to develop scurvy, even when the diet is entirely free from the antiscorbutic substance, and that its liver under these conditions is rich in this dietary factor. This species, therefore, is able to synthesize a single one of the dietary factors which are concerned with the etiology of the "deficiency" diseases. This is the only one which has been shown to be capable of originating *de novo* within the body, and only the rat and the western prairie dog of the United States have been demonstrated to possess this power. It is certain that man, monkey, and guinea pig, and apparently swine, cannot protect themselves against the development of scurvy, when the antiscorbutic substance is lacking in their food.

Under normal conditions growth follows definite laws, characteristic of each species, which determine the rate at which growth will proceed

from the time the ovum is fertilized. Continuity or discontinuity of growth at different periods in its history, the manner and extent to which the tissues differentiate and specialize with respect to function, as well as the ultimate size which the organism will attain, are determined by peculiar differences in the structure of the protoplasm of different species.

There is an optimum environment for the cells which compose the tissues, in which they will function most satisfactorily, and for the maximum time without developing faults in their mechanism, which we recognize as metabolic disturbances, by means or clinically recognizable alterations of function. Abnormal chemical reactions within the body lead to the excretion of products of perverted metabolism. Histological changes in the tissues, which may or may not become manifest later by gross anatomical changes, occur in certain conditions as scurvy, beri-beri, rickets and xerophthalmia. This environment, which is furnished by the blood, lymph, spinal fluid and other fluids of localized occurrence, with which the tissues are in contact, approximate most closely the ideal when the food supply is optimum in its composition.

There are safeguards to maintain the blood of satisfactory composition. The most efficient among these is the mechanism which preserves the neutrality of the tissues and body fluids. If the food is not of the most satisfactory kind the intestinal mucosa may exert to some extent a selective action in absorbing nutritive or other substances. The liver is very effective in transforming certain useless or toxic substances into harmless or less harmful bodies. The kidneys and the intestinal mucosa promptly excrete many substances whose presence in the environment of the living tissues are objectionable. These agencies are, however, of very limited efficiency and fail to maintain in all circumstances an optimum composition of the circulating and nutrient fluids of the body. It is not sufficient, therefore, that all the essential nutritive complexes and elements be present in the food. These should be introduced into the alimentary tract in the right proportions to meet the needs of the tissues. Either shortage or excess of one or another substance which is indispensable for the upkeep of the body may do harm. Even slight departures from the optimum in the character of the food supply, when maintained over considerable periods, leave their mark on the physiological well-being of the individual in a manner which can be easily recognized by appropriate methods of experiment. This fact has not been sufficiently recognized by clinicians or physiologists, and accordingly it is of special importance that we should illustrate the tendencies of faulty nutrition of a mild type, when persisted in, to cause disturbances of metabolism and perversion of function.

When any of the conditions essential for the normal development of an organism are sufficiently altered, growth is interfered with. The earliest interference with growth appreciated by physiologists was doubt-

less that due to lack of sufficient food. It is amazing to one who peruses the literature relating to nutrition during the last century to note how those physiologists who concerned themselves with the study of the nutrition of man or animals, failed to familiarize themselves with the effects of faulty diets of different kinds such as were producing scurvy, beri-beri and rickets in different parts of the world. The early chemists accomplished little because they tried to study foods by chemical methods. The physiologists accepted the view that the most important lines of investigation were energy values, digestibility, the optimum intake of protein and the extent to which foods of one class could replace those of another in the diet. It was not until recent years that an effort was made to determine by experiments on animals, the quality of foodstuffs, the factors which are indispensable in the diet, and the optimum conditions of nutrition which best support well-being.

A few years ago it was considered sufficient to carefully audit the food records to see that a satisfactory amount of energy and of protein were assured. To-day the guardians of the health of large groups of persons, as well as the mothers of households, are concerning themselves more with the question as to whether they are insuring those under their care sufficient amounts of "vitamines." The energetic manufacturers of pharmaceuticals are promoting in a more or less "ethical" way the sale of preparations said to contain generous amounts of the newly appreciated food factors, with alluring advertising matter telling what they are good for. Every physician should understand that this is quackery of the same grade as the fake remedies against which the American Medical Association has waged such effective warfare for many years. There is no place in therapy for concentrated preparations of "vitamines," even assuming that they are what they are purported to be. It is easily possible, by proper selection of foods, to prepare a diet which contains several times the actual needs of the body for any or all of these food substances. It is the duty of the specialist in nutrition to emphasize that the garden and the market, not the drug store, should supply us with these protective substances. This is the view that will ultimately prevail, but it will require time to establish it because of the prospects of money-making by the sale of this new type of remedy.

The ideal to be attained in nutrition during the period of growth is to afford the organism an optimum food supply to enable it to develop in a perfectly normal manner *uninterruptedly,* during both prenatal and postnatal life. This condition is seldom realized. Development is temporarily interfered with by diseases due to infection, which it is scarcely possible to escape during childhood. These impediments, as well as disturbances resulting from mechanical factors, and those in which there is disturbance of function of the endocrin glands, lie outside the scope of this chapter. Our discussion will be limited to those conditions

which arise more directly from faulty composition of the diet, either of the infant or child, or of the mother during gestation or during the nursing period.

The most important changes in our viewpoint relating to nutrition are the result of a better understanding of the chemical conditions which a diet must fulfill in order to promote growth, and of the specific dietary properties of each of the more important natural foodstuffs which enter into the diet of man. These have been acquired in great measure during the last ten years, and have enabled investigators to plan diets having but a single chemical fault. This fault may be chosen at will, or diets can be prepared which are faulty in respect to two or three dietary factors, each of which is definite and definable. Moreover, it is now possible to adjust these diets so as to make the quality with respect to the faulty factor or factors of any desired degree of intensity. By employing such diets, derived from any of a number of sources from among our natural foods, modified in special ways by the addition of purified food substances such as protein, inorganic salts, special preparations containing one or another of the unidentified dietary factors, it has been possible to conduct experiments on animals which have served to clarify our views regarding the effects of faulty diet on health and on the life history of the individual.

It may be stated definitely that experimental studies on animals have resulted in the definite imitation of so many of the conditions characteristic of malnutrition in man, that there is no room for doubt that the effects of deficient diets are the same in mammals generally. It has thus been possible to produce in animals, by diets in which the nature of the chemical fault is known, each of the deficiency diseases observed in man. This has given us an understanding of the relation of the diet to disease which has been a great revelation. This knowledge when applied to practical dietetics will be of inestimable service to humanity by preventing such conditions as arise through malnutrition.

The experimental results obtained during the last few years by Miss Simmonds and myself(*a*)(*b*) afford a basis for a full appreciation of the effects of faulty diets of different types on the well-being of an animal. These correlate so well with human experience that their bearing on the planning of the diet for the preservation of health and vigor, is of great service in educational work. They make evident that among the several factors which operate to influence health, the diet stands first in importance. They show clearly how far, when all factors such as temperature, illumination, ventilation and opportunity for exercise, are made uniform for a large animal population, and when no inequality is afforded by the surroundings for infection, the diet will determine the manner in which a young animal will develop physically, and perform the functions of adult life. A description of the experience of a large rat population in

our colony, with a series of diets comparable to the several types employed by man in different parts of the world, will serve to clarify the whole subject of the relation of the diet to development.

It has been shown by many tests that a diet consisting solely of cereal grains such as whole wheat kernel, maize, oat, barley and rye, together with the protein-rich legume seeds, peas and beans, and soy beans, fails, irrespective of its complexity or chemical composition, to satisfactorily nourish a growing animal. Even the above list of foods can be supplemented with fruits and such tubers as the potato, and such fleshy roots as the sweet potato, radish, turnip and beet, and with any desired amount of a muscle cut of meat such as round steak, ham, roast, etc., without making it satisfactory for a growing animal or for the maintenance of normal health and vitality in an adult. This list of foods forms the basis of a diet consisting of steaks, chops or roasts, potatoes, peas, beans, fruit, pies, etc., which is so commonly served in American homes at the present time. This statement seems most surprising but it rests upon an abundance of experimental evidence, not only with animals but upon human experience as well.

The faults in such a diet involve three and to some extent probably four dietary factors. The first in magnitude of importance is the shortage of calcium, and but little less serious from the physiological standpoint is the deficiency of sodium and chlorin. Next in importance is the lack of sufficient fat-soluble A to meet the needs of a growing mammal. The fourth dietary factor which is undoubtedly below the optimum in such a food mixture is that which may be designated as the antirachitic factor, because it is so intimately concerned with the development and functioning of the osteoblast, and consequently with bone development. When these faults in any seed, tuber, fleshy root and muscle meat mixture are corrected by suitable additions, it becomes a satisfactory diet for the promotion of growth and the maintenance of vitality.

It is possible to correct the inorganic deficiencies in a diet such as may be derived from the list of cereals, fruits, legume seeds, tubers, fleshy roots and muscle tissue, only by the use of liberal amounts of milk or of leafy vegetables, or by the direct consumption of bony substance or other source of calcium such as the carbonate, together with common salt. The omnivorous and herbivorous animals follow one of these practices for the completion of their diet, or fall below the normal level of nutritional stability within a short time. The carnivorous animals and carnivorous man secure the same result by the consumption of blood, which is rich in sodium chlorid, and a certain amount of bone for its calcium, and enrich their food with fat-soluble A by ingesting glandular organs, which are good sources of this dietary factor. The leaves of plants and the fat of milk, butter fat, are also excellent sources of this dietary essential.

The statement made in the preceding paragraph may be put in an-

other way by saying that there are but three types of diets which succeed in the nutrition of man or animals. One of these is the strictly carnivorous diet such as certain of the Eskimos, the American Indians, the natives of Iceland until a generation ago, Laplanders, Patagonians and others subsisted or still subsist on. Judged by their physical development these peoples are about as successful in their nutrition as are the carnivorous animals such as the lion, tiger, wolf and others. Success with this type of diet depends upon the consumption of a sufficient amount of the glandular organs, bone marrow, bony tissue, blood, etc., as well as of muscle and fat. Confinement for a few weeks to a diet of muscle tissue (steak, ham, chops, etc.) alone, which represents the type of meat eating which appeals to the people of America at present, will do great harm.

The second type of diet which succeeds is that consisting of cereal grains, legume seeds, tubers and meats, supplemented with liberal amounts of leafy vegetables. The vegetative parts of plants, the leaves and growing tips of stems, contain everything that is essential for the nutrition of an animal. Many species and herbivorous animals subsist throughout the normal span of life on grass or other leaves, with or without seed grains. They cannot long survive on a diet restricted to the storage tissues of plants, such as seeds, tubers and fleshy roots. The leaf, or vegetative part of the plant has decidedly different dietary properties from the reproductive parts, containing as they do much reserve food material.

The third type of diet which is satisfactory for the maintenance of normal growth and well-being is that in which seeds, tubers and meats are supplemented with liberal amounts of milk. Provided a sufficient portion of the food mixture, a fraction which has as yet not been satisfactorily determined, consists of milk, the selection of the other components and their relative amounts are without much significance, since the dietary properties of cereals, legume seeds, tubers and muscle tissue meats are similar.

The widespread practice has grown up of marketing for human consumption the degerminated and decorticated cereal products such as bolted wheat flour, polished rice and degerminated corn meal, instead of the whole kernel ground to a flour or meal, as was formerly the case. This practice resulted from the necessity of increasing the keeping qualities of bread grain products owing to the long period required for transportation and marketing at the present time. The substitution of these milled products for the entire grains is unfortunate, because the dietary defects of the seeds from which they were prepared are markedly accentuated. Modern marketing on the scale made necessary by the growth of the urban population requires that such products be manufactured and that they continue to enter into the human diet in considerable amounts. This makes it more urgent now than formerly, that the other articles in

the diet be carefully chosen in order that sufficient amounts of the "protective foods," dairy products and leafy vegetables, enter into the daily menus to correct the deficiencies of the remainder of the diet.

If we restrict a young rat for a time to a diet of cereal grains, legume seeds and muscle meats, with or without tubers and other storage tissues of plants, it will fail to grow; will develop rickets, and at an early age will die. As stated above, the nature of the deficiencies in this diet are well understood to be lack of sufficient calcium, phosphorus, sodium, chlorin and fat-soluble A. When sodium chlorid, calcium phosphate and butter fat, or other fat having similar dietary properties (cod liver oil, egg yolk, etc.) are added, the diet is made satisfactory and the animals develop normally and go through successive generations without deterioration in stamina.

It is obvious that if the amount of protein in the diet is sufficiently low to fail to supply the necessary material for the construction of new body tissue, growth will be interfered with. A condition at least approximately similar arises when the protein in the diet, though abundant, is of inferior quality and therefore not effectively transformable into body proteins. Both of these conditions may and do arise in human experience. Under such a dietary regimen there is maintained a long lithe form, even though growth may be suspended for a considerable period. No statistical data have been collected to show whether rats in this condition, as the result of error in the protein factor as an uncomplicated fault, causes changes in the form due to lengthening of the body and limbs, even when there is no increase in body weight. If this is what happens, the changes described would correspond in great measure to those described by Aron, Waters, and Trowbridge as the result of underfeeding with a diet of such a character as would induce growth and normal development provided the amount of food available were sufficient.

There are changes in form which are very characteristic when the diet is faulty in certain other respects. This is especially true of diets deficient in calcium. Even when the diet contains everything else that is necessary for the normal development of a mammal, but the calcium content falls below the optimum, although not to an extent to interfere with growth, the first generation of animals may look fairly normal, but will age early. Their fertility will be low and infant mortality high, and the few young which grow up will exhibit deformities which prevent their reaching the full adult size. They are short and stocky, with deformities especially of the ribs and spine. The displacement of the viscera downward owing to the contraction of the thorax gives them a pot-bellied appearance. The damage done by such a diet is permanent, for recovery with expansion to the normal figure is not possible even when the faults in the nutrition are corrected while the animals are still young chronologically.

It is perhaps most convenient to discuss in this connection the effects of undernutrition, in the sense of lack of sufficient food to meet the caloric needs of the body, as well as a relative lack of sufficient amounts of several dietary factors due to restriction of the intake of food. Such studies have been carried out by Aron(*a*) with dogs, and by Waters(*a*) and Trowbridge(*a*) with cattle.

In Aron's experiments young pups from the same litter were divided into experimental groups, one of which was fed liberally on a mixed diet, so as to cause at least approximately optimum development. The other group was fed the same diet, but the amount of food was adjusted so as to maintain the body weights constant for about a year. The control animals trebled their weights during this interval. The results indicate that when the food supply is inadequate in amount but satisfactory in quality for the maintenance of nutrition at a plane at which there can be no increase in weight, the body is not merely in a condition in which there is lack of growth, but of starvation, and is actually undergoing changes in composition in which a portion of the fat and muscle tissue components disappear and are replaced by water. When increase in weight is inhibited by restriction of the food supply, the skeleton grows at the expense of certain of the soft tissues, especially the muscles. There is therefore, a pronounced alteration of form, but the glandular organs and the brain retain their weight and size. Indeed, the brain appears to grow at about the normal rate to approximately the normal size under these circumstances.

Under the conditions described the body fat disappears in great measure through oxidation, and the proportion of the entire body substance composed of water is markedly increased. The caloric value of a gram of body tissues, sampled so as to represent the entire mass of tissues of an animal which has undergone such a change, carried to the extreme limit, may amount to only about one third of the normal value (Aron).

When the control animals had trebled their original weight, Aron fed certain of the stunted pups *ad libitum* and found that while they were able to round out their forms through fattening, and through enlargement of the muscle fibers, they were unable to develop the normal form. During the period of stunting, the growth was largely due to changes in the bones, and these, according to Aron, lose their capacity to grow as age advances, regardless of the size which the animal has attained.

Aron deduced from such experimental evidence, that an infant which does not increase in weight, or does so very slowly, is so undernourished that a portion of its body substance is being consumed. This would seem to be too sweeping a conclusion. There are doubtless a number of conditions under which an infant may not increase in weight, for a time, when it is actually taking sufficient nutriment to support growth, provided it were not handicapped by some factor aside from nutrition. It is, of

course, always easy to calculate from the amount of food consumed by an infant whether it is taking sufficient food to support growth, or whether it is on a maintenance or submaintenance diet so far as energy values are concerned.

Rosenstern urges, reasoning on the same basis, that a child of a weight considerably below that which corresponds to its age, will need a higher intake of calories per kilogram for an increase in weight due to symmetrical growth than either an infant of the same weight but younger, or one which is of the same age but heavier, i. e., normal in weight. Finkelstein(*c*) (cited by Aron) advises that a child be given the number of calories corresponding to its age, irrespective of its weight. Such a generalization presupposes, naturally, that inhibiting factors other than lack of sufficient food are discovered and eliminated.

Osborne and Mendel have shown that rats fed *ad libitum* on diets which were satisfactorily constituted except that the amount of protein was so small as not to permit of growth, or the protein was present in relative abundance but was of such poor quality that only maintenance without growth was possible, could be maintained at constant weight for surprisingly long periods, in terms of the span of life of the species, without their losing their capacity to grow. When the diet was corrected the animals grew at a rate faster than the normal, but failed to reach the maximum size which might have been reached under better conditions of uninterrupted nutrition. It is not warranted, as has already been indicated, to generalize from these observations, concerning the retention of the capacity of an animal to grow after periods of suspension from any cause. In the case of calcium at least, we have a dietary factor of which it is of the utmost importance to maintain an uninterrupted satisfactory ingestion, for a temporary suspension of growth due to lack of this element leads to permanent deformity.

It is possible, in the light of experience in experimental work with the rat, to start with a diet consisting of degerminated cereal products such as bolted wheat flour, degerminated corn meal, and polished rice, the remainder being made up of peas, beans, potato and rolled oats or other foods having similar dietary properties, and to so modify it in a series of experiments that the span of life, fertility, development of the sucklings, infant mortality and age at which signs of senility appear, can be made almost anything we desire. The mixtures described, irrespective of the proportions in which they are combined, will not support any growth whatever in a young rat. The deficiencies have been shown to be a lack of sufficient calcium, phosphorus, sodium, chlorin, fat-soluble A, and low biological value of the protein mixture. The importance of the several factors named are in the order given.

If we systematically enhance such a standard mixture with respect to the factors named, but in limited degrees, in a series of

experiments, making each diet better in respect to the faulty factors than the one which preceded it in the series, we can regulate the rate and extent of growth of the several groups of animals and profoundly modify their life histories. It is especially significant that a series of diets may all be of sufficiently high quality to permit of approximately normal growth to the adult size, and the animals may present a good appearance during growth, yet the slight faults in these diets may lead to early loss of vitality, early aging and inability to succeed in the nursing of the young. This last function is of special importance in connection with the present discussion.

Several situations may arise in such experiments. The mothers may react unfavorably toward their young and destroy them soon after birth; they may try to nurse them but because of inadequacy in the composition or amount of milk secreted, fail to induce the proper rate of growth in them. The evidence seems to support the view that long before the milk supply falls off to a point sufficient to arrest growth in a suckling, the quality of the milk has been sufficiently lowered to interfere with growth, even though the energy requirements of the young are met. McCollum and Simmonds(*a*) have studied this problem in the rat and have shown that when the diet of a nursing female is faulty, with respect to any one of several factors, the young will not grow as they should, and may even die after an interval of malnutrition. It was found that after the growth of a litter was suspended for a time by this method, they could be made to respond with growth within forty-eight hours in many cases by correcting the diet of the mother. In this manner they tested lack of sufficient calcium, of fat-soluble A, of water-soluble B and of protein, as the single and sole deficiency in the mother's diet, and in each case the quality of the milk was seriously affected.

This observation has an important bearing on the problem of the diet most suitable for the human mother during lactation. It is food for thought that in no instance with an animal as a subject has it been possible to succeed in the nursing of young, on a diet consisting of cereal grains, legume seeds, tubers, and muscle meats. The failure is even more decided when a considerable amount of degerminated cereal products such as wheat flour, corn meal and polished rice enter into the composition of the food mixture. Is it not important that the nursing mother should take regularly a diet of better quality than the type which is now so commonly adhered to, viz.: one consisting in great measure of bread made from bolted flour, muscle cuts of meat and potato?

According to the investigations of the American Pediatric Society, ten cases of scurvy out of a total of 356 were in breast-fed children. Beriberi is not infrequently seen in infants who nurse mothers who are suffering from the disease. Rickets have been many times observed in children who are breast fed. The causes of these diseases are well understood.

They involve specific starvation or partial starvation for specific dietary factors which are essential for the maintenance of normal metabolism, and the type of pathological condition which develops is characteristic for each of the three factors in this class of nutrient principles whose existence has been definitely established. There is no instance known where xerophthalmia has resulted in a breast-fed infant, or in a nursing animal as the result of a lack of the substance, fat-soluble A in the diet of the mother, and consequently in the milk. Miss Simmonds and I have, however, definitely proven that the factor in question is not present in the milk unless it is furnished in the diet of the mother. Diets deficient in fat-soluble A may in certain instances lead to nutritional disturbance in human infants, although this must be very uncommon. There is much reason to believe, on the other hand, that deficiency of this factor to a degree which brings the infant or older child into a state of nutritional instability, and contributes to the severity of the effects of other deficiencies such as lack of calcium, low protein, etc., is by no means uncommon.

The fact that the "deficiency" syndromes develop so rarely in infants which are nursed should not be interpreted as an assurance that all is well with the nursed infant so far as the composition of the food supply is concerned. *For every child which actually develops a condition which is clinically recognizable, there are many which reach the stage of borderline malnutrition of a more or less specific type.* As a rule two or more dietary factors are sufficiently below the optimum in quality to cause damage which will in the course of time become recognizable in some manner.

The prominence which the unidentified dietary factors, popularized under the term "vitamines," have had in discussions of nutrition during recent years has tended to mask the importance of other factors of equal significance to health. Chief among these is calcium. There is much evidence that the calcium intake of the breast-fed infant is as a rule not far from the minimum on which normal growth can take place. This is made clear by the occurrence of rickets with such frequency as to make the disease a national health problem in the United States and in most of the countries of Europe at the present time. Calcium and phosphorus are two of the factors which play a prominent rôle in the etiology of rickets. Another factor is an organic substance, whose chemical nature is not known, but which is normally supplied by milk in sufficient amounts to meet the needs of the developing child. There is much reason to suspect that milk, even when of good quality and produced by a lactating female whose diet is satisfactory according to our ordinary standards, does not contain enough of the antirachitic factor to give an appreciable margin of safety. When the diet of the mother is not well chosen, this is one of the factors in which its quality is most likely to fall below normal. The antiscorbutic factor in milk is also not ordinarily sufficiently abundant to much

more than meet the actual requirements of the growing child, and it is equally important that the diet of the mother be chosen so as to furnish a satisfactory amount of each of these two substances.

There is the greatest need for an appreciation of the dangers of borderline malnutrition in children. This is rare indeed among medical men. It is time that the profession should understand the progress which has been made in the investigation of nutrition, which has made possible the accurate estimation of the quality of each of the important components of the diet. This in turn allows the specialist in nutrition to predict that certain combinations of natural foods will have certain shortcomings, and will fall short of the optimum in the nutrition of an animal. It is no longer justifiable to form judgment as to how well an infant is nourished, by its growth or by its appearance. The only safe way is to make those who are responsible for the welfare of the infant familiar with the principles by which quality in milk or other foods is to be judged, and it is their duty to make certain that the diet is of such a character as to promote growth and development in an optimum manner. It is the life history which we are to consider, and not the rate of growth during the months of infancy. We must attain our goal of making the diet of every infant of such a character as to afford uninterrupted and optimum development to its adult size. This will fortify it against unfavorable influences of various kinds which may react upon its well-being in later life.

The Metabolism of Traumatic Shock . . . . . *Joseph C. Aub*

Theories of Shock—Pathological Physiology of Shock—Acidosis in Shock—Basal Metabolism in Shock—Chemical Changes in the Blood in Shock—Summary—Treatment of Shock.

The Metabolism of Traumatic Shock

JOSEPH C. AUB

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Traumatic shock is an acute, abnormal state which must always be of interest to the surgeon, not because of its frequency, but because of its serious prognosis. Its frequency, as seen upon the battlefield, probably explains the large amount of study upon the subject which accompanies each war; and yet the condition is not an unusual accompaniment of civil life. For example, the surgical statistics of five representative hospitals for five years show that 19 per cent of the total 2,703 deaths were complicated by "shock."

Traumatic shock may be divided into two types. There is primary shock, which appears promptly after the accident or trauma. It is most often seen after abdominal or cranial injuries, and, while its appearance is quite similar to that seen in secondary traumatic shock, its onset is prompt, its cause probably in the central nervous system, and its prognosis very grave. Very little is known of this form of shock; the onset is so rapid and the condition so serious that it is a difficult state to study. Much more is known about secondary traumatic shock. This usually develops gradually some time after the trauma, and it is most often associated with wounds involving large muscle masses.

The characteristic picture of shock is a patient lying quietly, or mildly restless, usually with dulled mentality, and with slow reaction time, and frequently not conscious of much pain. The face is pale, with a dusky pallor, sunken eyes, and drawn expression. Respiration is slightly increased in rate, superficial in volume, and made irregular by occasional deep sighs. The pulse is rapid, very soft, and often difficult to obtain. A low blood pressure is the most distinguishing feature of the condition. It is, usually, almost a quantitative index of the severity of the shock, falling in very severe cases as low as 50 mm. Hg systolic, or even so low that it is impossible to feel the pulse or hear the impulse in the arm. The body temperature is also reduced, frequently to 94° or 95° F., and even to 87.8° F. in spinal cord injuries. The surface of the body is cold and is usually drenched with perspiration. Indeed, the whole appearance is one very closely resembling severe hemorrhage, or an

overwhelming infection (such as gas gangrene). The differential diagnosis of the primary condition is, therefore, often a difficult one.

Theories of Shock

Many attempts have been made to explain the phenomena found in shock, and there are many theories as to its cause. Crile (*b*) believes that painful stimuli cause an exhaustion of the cells of the central nervous system, and that a resulting failure of the vasomotor center causes the low blood pressure. Yandell Henderson (*a*) thinks that the excessive stimulation and pain cause hyperpnea. As a result there is a marked reduction of CO_2 in the blood, and this in turn induces vasodilatation and a fall in blood pressure. Porter has advanced the theory that trauma releases fat droplets into the circulation—droplets which cause fat emboli in the lungs and central nervous system, and lead to a fall of arterial blood pressure by preventing venous return to the heart, and by affecting the higher nerve centers. Cannon and Bayliss, in a series of very interesting experiments, showed that shock could be produced by crushing large areas of muscle tissue. A fall of blood pressure followed the crushing in about twenty or thirty minutes and was usually progressive. Shock developed even though the wounded area had its nerve supply cut, but did not develop if the blood supply was tied. The conclusion from these experiments was that shock was a toxemia, due to some substance arising in the injured tissues. At about the same time that these experiments were in progress, Quénu and his collaborators were arriving at a similar conclusion, by investigations on soldiers wounded at the front.

Pathological Physiology of Shock

From this brief review of the theories of the cause of shock, and of the accompanying phenomena, it becomes clear that the primary cause of the condition is far from being determined. This, however, is not true of the various phenomena which may either precede or accompany the development of traumatic shock. Great advances have been made in our knowledge of these conditions during the past few years, largely during the last two years of the recent World War. The wisest procedure is probably to study the various accompanying phenomena in the order in which they occur. The most striking phenomenon which has been observed for many years in shock is that the patient seems quite exsanguinated. Previous to the recent war it was generally considered that the blood was stagnating in the abdominal vessels. The testimony of many surgeons, who had large experience during the war, was that the blood was not in

the large veins of the abdomen, that these veins, in fact, appeared quite as devoid of blood as the vessels of the rest of the body.

Where, then, is the blood? The first work which offered a suggestion for the answer of this problem was done by Cannon and collaborators in Béthune. They found that the blood in the capillaries of the periphery was more concentrated than that in the veins, and that the red count from these capillaries was very much higher than the count taken from the veins. This suggested that the fluid of the blood was leaving the circulation and going into the tissues. That the volume of blood actually does decrease has been very beautifully shown by Keith on human beings, and by Gasser, Erlanger and Meek on animals. These latter observers have also shown that the protein content of the plasma is not changed by the process of concentration. It therefore seems clear that the plasma as a whole leaves the circulation. This reduction of blood volume which has still not been explained may of itself explain the resulting phenomena which develop.

The first effect of the diminished blood volume seems to be to affect markedly the blood flow to certain parts of the body. Gesell (*b*) showed in very interesting experiments the marked slowing of blood flow through the salivary glands, not only in shock, but also following the withdrawal of blood, even when this did not lower the blood pressure. This fact suggests that the resulting vasoconstriction, though satisfactory in keeping up the blood pressure to its normal level, still has as an effect the marked slowing of the blood flow at least through some tissues. If the blood volume continued to fall, the next effect was a drop in blood pressure. Wiggers also showed, by optically recorded blood pressure studies, that the effects upon the circulation in shock might appear before a low blood pressure level was reached. As the blood volume continues to decrease a fall of blood pressure results, which may reach the low level of 50 or 60 mm. Hg, frequently found in shock. With this fall in blood pressure, and the resulting decrease in the force of propulsion through the capillaries, the blood flow naturally continues to decrease in speed. One effect of this slowed blood flow and reduced blood volume must be to reduce the amount of oxygen available for the use of the tissues.

That the oxygen available for the tissues is markedly reduced in shock was first demonstrated by Yandell Henderson (*a*). He showed that in experimental shock the venous blood had far less oxygen than had the venous blood before shock, and arrived at the conclusion that the oxygen supply available was inadequate for the tissues. This work has been recently confirmed by Aub and Cunningham, who also found that this decrease in available oxygen is seen before the blood pressure reaches the shock level of 80 mm. Hg. Fig. 1 pictures graphically the magnitude of this change in the venous oxygen content. By mechanically preventing the normal blood flow through increasing pericardial tension, Aub and Cun-

ningham showed that the same effect was obtained as in shock, and that, therefore, the probable explanation for the diminished oxygen content of the venous blood lay purely in the mechanical slowing of the blood flow. While these phenomena are all occurring during the development of shock, and are present to a more or less marked degree before the blood pressure has fallen very low, it is only when the pressure falls below

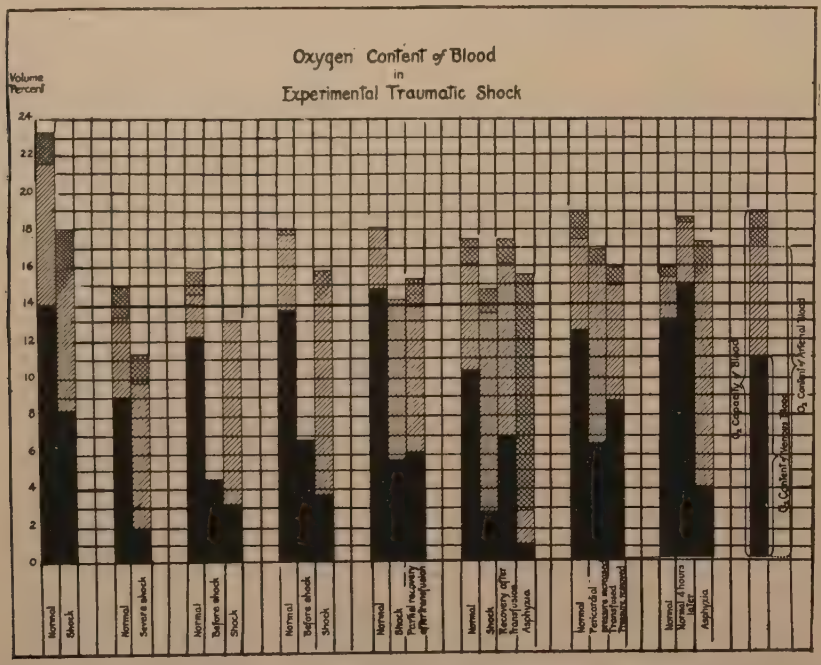

Fig. 1. "Normal" means a cat under urethane anesthesia; "Before Shock" means after muscle injury, but before a true shock level of blood pressure has been established. The oxygen content of the venous blood is markedly reduced. (From Aub and Cunningham.)

80 mm. Hg that most of the other phenomena accompanying shock are found. Cannon has therefore called 80 mm. the "critical level" of blood pressure in this condition, the probable explanation being that until that level is reached the blood flow and the available oxygen are sufficient to accomplish the normal oxidation required in the tissues.

Acidosis in Shock

That there is diminished alkali reserve in the blood in shock conditions has been repeatedly shown and confirmed. Crile reported cases which suggested acidosis in shock. Cannon (*c*) reported the finding of a decreased alkali reserve in shock. He used the method of Van Slyke,

and found that the alkali reserve began to fall below normal, only when the blood pressure fell below the critical level of 80 mm. Hg. Henderson in 1910 suggested that the probable explanation for this diminished alkali reserve lies in the inadequate supply of oxygen to the tissues, and in the resulting abnormal metabolism. The actual explanation is still under discussion. Henderson believes that the decreased alkali reserve is not due to an accumulation of acid bodies, but rather is due to the disappearance of the reserve alkali into the tissues. According to this theory, shock is due to marked hyperpnea and a resulting loss of too much carbon dioxid, thus causing an accumulation in the blood of an extra amount of reserve alkali. He believes that this excessive alkali leaves the blood stream and migrates into the tissues, or is excreted by the kidney. As a result, a diminished alkali reserve is found. Many investigators, however, believe that the diminished alkali reserve is due to an accumulation in the blood stream of acids formed because of an inadequate oxygen supply during the metabolism of body tissues, and recently Macleod has shown the presence of abnormal quantities of lactic acid in the blood plasma of cases of shock.

Basal Metabolism in Shock

It might well be expected that, with the decreased oxygen available for tissues, the normal rate of metabolism could not be maintained. The marked loss of body temperature seen in shock suggests likewise that the metabolism is not adequate to maintain the normal body heat. No work on this subject has been possible in man. Henderson, Prince and Haggard mention that there is a marked drop in metabolism in shock. Aub, working on cats, found that with the development of shock there was a marked fall in the rate of the basal metabolism as studied by the respiratory gas exchange. The temperature in these experiments was kept as constant as possible, so that the change in metabolism was not due to a drop in temperature. In mild cases of shock the metabolism fell to a level averaging 19 per cent below that found before shock was induced; and in severe cases of shock the metabolism fell 30 per cent below that found in the intact anesthetized animal. This drop in metabolism was roughly parallel to the severity of the shock, and usually did not appear until the blood pressure had fallen to 80 mm. Hg or below.

That the fall in metabolism was dependent upon the inadequate blood flow was readily shown by experimentally producing slow blood flow by increasing pericardial tension. This method, which does not induce a true shock, but mechanically lowers the blood pressure, caused a similar drop of about 30 per cent in the basal metabolism of the experimental animal. The fall in basal metabolism, therefore, seems to be due to an

inadequate blood flow and oxygen supply, and not to any other toxic factor. When recovery from shock was obtained by the use of blood trans-

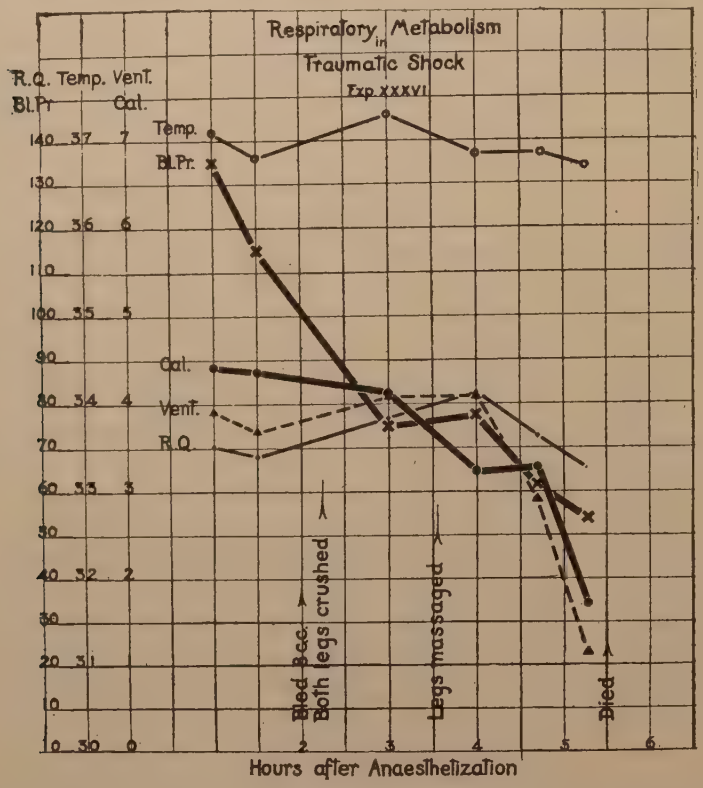

Fig. 2. An example of the respiratory exchange in the cat in experimentally produced shock. Blood pressure (Bl.Pr.) was used as the index of the severity of the condition. The calories used per hour (Cal.), Ventilation per 100 c.c. per minute (Vent.) and Respiratory Quotient (R.Q.) are shown graphically before and during the course of severe shock. (From Aub.)

fusion, and the blood pressure was raised above 80 or to a normal level, the metabolism tended to return to the original rate.

Chemical Changes in the Blood in Shock

With the marked change in blood flow and the decreased metabolism already described, and with the decreased urine output, due probably to the reduced blood pressure, it is to be expected that there would be marked chemical changes in the blood plasma. Govaerts first noted an intense leukocytosis with large war wounds. Brodin and Saint Girons judged this to be the response to the absorption of products produced about the injured tissues. Duval and Grigaut studied the non-protein

nitrogen of the blood, and concluded that there was an increase in the non-protein nitrogen which started promptly after the wounding, and was at its height during the second day, and then gradually returned to normal. This increase was slight in unshocked cases but was striking in cases of shock. This retention occurred, not only in the urea portion of the blood, as in nephritis, but also in the remainder of the non-protein nitrogen. Aub and Wu likewise demonstrated a marked increase in the non-protein nitrogen of the blood in experimental shock, and found that the creatin portion of the non-protein nitrogen was increased in far greater proportion than was urea or the total non-protein nitrogen. This change in the non-protein nitrogen of the blood appeared only when shock developed. In control experiments where blood pressure and blood flow were reduced by increasing the pericardial pressure, the values for non-protein nitrogen and creatin were not markedly changed. In the experiments where muscle trauma was inflicted but no shock developed, there was likewise but slight change in the non-protein nitrogen. When shock developed, however, the amount of non-protein nitrogen in the blood rose markedly, and the values for the creatin were sometimes three times as high as before trauma had been inflicted. This marked rise in creatin was taken as direct evidence of the presence in the blood of products of muscle necrosis, and was, therefore, considered suggestive evidence for the theory of a chemical cause of traumatic shock.

The blood sugar is likewise increased in shock. This was first noticed by Cannon in wounded soldiers who were in shocked condition; it was also observed by Aub and Wu in experimental traumatic shock in animals, where it occurred to a much greater extent than was present in man. It is difficult to explain this rise in blood sugar.

Very little work has been done on the urine in shock, probably because of the acute onset of the condition and the difficulty of getting satisfactory specimens. Mestrezat, working on a few cases, did a nitrogen partition of the urine, and found that the rest nitrogen, other than urea, was in much greater proportion to the total nitrogen than usual. This is in agreement with the changes described in the non-protein nitrogen of the blood.

Summary

From the evidence cited above it seems that the sequence of events in traumatic shock is as follows: There is first a slowing of the blood flow, probably accompanying a decrease in blood volume. This decreased blood volume and blood flow as they progress become so great that vasoconstriction can no longer maintain a normal blood pressure. The blood pressure then falls, and a condition of anoxemia or inadequate oxygen supply is present in the tissues. With this anoxemia, there develops a diminished

alkali reserve, and also a diminished total metabolism. At the same time that there is a diminished metabolism, there is an accumulation in the blood of non-protein nitrogen and particularly of creatin, which suggests that products of muscle necrosis are appearing in the blood stream. None of the constituents analyzed are in the least toxic, or could be the *cause* of shock, yet it is possible that some other chemical substances may accompany them into the blood stream which may be toxic in their action, some such substance possibly as histamin, which has been extensively studied by Dale and Laidlaw (*a*) as the cause of one form of shock.

Treatment of Shock

From these considerations, the treatment usually recommended in shock becomes logically indicated. With the reduced temperature so distinctly seen in the condition, and with the reduced metabolism, which has been demonstrated, it is clear that warming the body by outside heat is indicated. It is, therefore, wise to maintain body heat as near normal as possible, and if it has fallen, to raise it promptly to its original level. This can most readily be done by a hot air bath and hot water bottles, but great good can be accomplished by giving very warm and large drinks of fluid; and strong coffee with its stimulating effect seems to be beneficial. The second important indication is to increase the blood volume. This may be very readily accomplished by forcing fluids by mouth and rectum, as shown by Robertson and Bock. If vomiting is present, fluids must be forced—preferably by rectum—but they may also be given intravenously. But in severe shock with low blood pressure where it is important for the vital centers to have the blood pressure promptly raised, immediate transfusion is of great value. Blood is the medium of choice, and if it can possibly be obtained should always be used. If blood is not available, however, the gum acacia solution suggested by Bayliss (*a*) is the next choice, since it maintains a normal blood pressure for a far longer period than will saline solution. Raising the blood volume is of the utmost importance, and associated with the transfusion of blood, one should never forget that forcing fluids over a long period of time is of great therapeutic value. These fluids, of course, should be *warm*. Giving large doses of morphin is usually recommended, but except to quiet the patient, the logical reason for its use is difficult to understand. The first treatment of shock should take the form of preventive measures, and particularly in hospitals where patients can be watched from the beginning, a severe prolonged shock should never be allowed to develop. As the blood pressure begins to fall, prompt action in forcing fluids and in applying warmth should be instituted to keep the blood pressure above the critical level of 80 mm. Hg.

The treatment of the metabolic conditions accompanying traumatic

shock are thus associated, first, with maintaining the blood volume at a fairly normal level, and secondly, with maintaining the body temperature of the patient. In cases where hemorrhage is involved, it is important that it should be stopped before transfusion is attempted.

A tourniquet bound for some time about an injured extremity is to be regarded with dread, because its removal may, and occasionally does, precipitate a severe shock, due probably to the sudden release into the blood stream of toxic substances. If the extremity is to be amputated, it is much wiser to leave the tourniquet in place and to operate above it.

After Care.—The care of a case in shock does not end with the return of the blood pressure above the critical level. Fluids should be forced for several days—or until the output nearly equals the intake—for blood transfusion does not usually bring the blood volume to normal level. The patient's temperature must likewise be watched, and artificial heat continued, if necessary. Infections in convalescence are quite common, and it is important to watch and guard the patient against them.

SECTION II

Special Pathological Metabolism

Pathological Metabolism of Diabetes Mellitus . . . . . *Rollin T. Woodyatt*

Introduction—Glycosuria—Diabetic Glycosuria—Sugars Other than Glucose in Diabetic Urine—Mechanism of Glycosuria—Diabetic Glycosuria—Total Metabolism in Diabetes—Sources of Glucose Supply—Carbohydrate—Protein—Fat—Deductions—Cause of Under Consumption of Glucose in Diabetes—Cause of the Impaired Glucose Utilization in Diabetes—The Nature of the Internal Secretion of the Pancreas—Acidosis—Dietetic Management of Diabetes—Rationale of Dietetic Management—Endogenous Factors of Food Supply—Dealing with the Food Supply in Terms of Carbohydrate, Protein and Fat—Discussion of Hypothetical Diets—Estimation of "Optimal" Caloric Diets—Remarks.

Pathological Metabolism of Diabetes Mellitus

ROLLIN T. WOODYATT

CHICAGO

Introduction

Diabetes is a condition. The diabetic patient is an individual. An individual with diabetes may be of either sex, any age, probably of any race, and he may have any grade of diabetes—from the most complete known to a grade so slight that it is not certainly distinguishable from the normal. An individual by virtue of his diabetes is not thereby protected from the deleterious effects of physical or chemical forces, nor is he immune so far as we know to any type of infection, nor is diabetes necessarily incompatible with the development of new growths or the coexistence of other anomalies of the metabolism—such as exophthalmic goiter, gout, obesity, acromegaly, Addison's disease, etc. On the contrary, diabetics in general are a group in which other diseases abound. The subject of diabetic individuals is as broad as medicine. Only diabetes itself—the condition—lends itself to special discussion. These platitudes may be forgiven in view of the manifest confusion that is created in the literature by a rather widespread tendency to describe under the heading diabetes many disease conditions and metabolic disturbances in which the diabetes itself is not pure or in which indeed it may not even be the most important factor, or in which the diabetic anomaly is given a peculiar expression because of some complication. Thus an inherently mild case of diabetes in the throes of a passing epidemic infection may be classified as a case of ultra severe diabetes and the resultant anomalies of the metabolism due partly to diabetes and partly to the infection may be attributed simply to the former. It is not always possible to distinguish between "pure" diabetes and complicated diabetes since the etiology of the disease is obscure. Yet in studying the anomaly of the metabolism, a selection of stationary and apparently uncomplicated cases will form the solidest basis for departures.[1]

[1] In penning the following pages the attempt has been made to adhere as closely as possible to the discussion of anomalies of the metabolism that characterize such cases.

Glycosuria

Whereas the normal urine at all times contains reducing substances and substances which are optically active, which yield crystalline compounds with the hydrazins and respond to other tests as sugars do, these substances are not all sugars nor are all the sugars glucose. The quantity of fermentable reducing substance in normal urine averaged about 4 parts in 10,000 (0.04 per cent) according to Lavesson. Bang and Bohamannson estimated the total reducing substance in the urine of normal adults as between 0.21 and 0.24 per cent, of which about 18 per cent was fermentable (0.038 to 0.043 per cent of fermentable reducing substances). Benedict, Osterberg and Neuwirth found an excretion of fermentable reducing substance ranging between 0.903 and 1.161 gm. in twenty-four hours in the case of a normal adult on an ordinary mixed diet. During a fast it approached zero, according to these writers, and on a diet low in carbohydrate it averaged 0.75 gm., while with a high carbohydrate diet it rose to 1.5 gm.

The term glycosuria means the passage of glucose in the urine and it would follow that glycosuria is a normal phenomenon. However, the term was first used in connection with the abnormally increased glycosurias of diabetes and, as it appears in the medical literature without qualification, it is commonly intended to mean an excretion of more than the normal quantity of glucose. As it has been expressed by Naunyn(*c*) "Wenn wir schlechthin von Glykosurie als einer krankhaften Erscheinung sprechen so meinen wir freilich die über die norm gesteigerte Glykosurie; während auch in der Norm der Urin (des Menschen) eine ganze geringe Menge Zucker, und zwar Traubenzucker (Glykose) enthälte. Aber auch die über die Norm gesteigerte Glykosurie kommt ohne Diabetes vor."

What then constitutes a normal glycosuria and what is to be regarded as abnormal? A custom in the clinic is to test the native urine by means of one of the well known qualitative sugar test solutions. A positive test is then used as the criterion of an abnormal quantity of reducing substance, a negative test of a normal quantity. But the positive or negative result depends on the delicacy of the test as performed, on the concentration of the reducing substance in the specimen and on the quantity of interfering substances. In border-line cases the simple qualitative copper test is capable of giving false impressions. The error arising from method and variations of the urinary volume may indeed be obviated in a measure by bringing the urine for 24 hours to a standard volume of 1, 2 or 3 c.c. per kg. of body weight per hour of secretion and always performing the test in the same way, but a truly quantitative method is to be preferred. Benedict and Osterberg(*b*)(*c*), working with a new method for the quantitative esti-

mation of sugar in normal urine, emphasize the fallacies of the ordinary clinical test. In border-line cases this procedure is of great value in settling the question of the quantity of sugar excreted. However, having done so, it still remains to be settled whether the quantity found is normal or abnormal. It is obvious that the size of the individual must be considered, the time of excretion and also the rate at which glucose is entering the metabolic stream. For a man weighing 75 kg. a total excretion of 1500 mg. per kg.; for one weighing 50 kg., it is 30 mg. per kg. An excretion of 20 mg. per kg. in 6 hours is at the rate of 80 mg. per day. Also an excretion that is normal for one normal rate of glucose supply may be excessive for a lower normal supply rate, etc. For a true interpretation of glycosuria it is necessary to consider the entire curve of glucose excretion by normal subjects under a series of supply rates. Benedict and Osterberg(*c*) found the total sugar excretion, fermentable and unfermentable, for an 18 kg. dog on a mixed diet to average 17 mg. per hour (i. e., 1 mg. per kg. hour). In fasting the fermentable fraction almost or quite disappeared and the total sugar fell to 4.7 mg. per hour (0.26 mg. per kg. hour). Benedict, Osterberg and Neuwirth working with a normal man (body weight 86 kg.) on mixed diets saw an excretion of 0.903 to 1.161 gm. of sugar per day, average 1 gm. per day. The same man on "an empty stomach" excreted 79 mg. in 2 hours. The ingestion of 20 gm. of glucose then caused no increase of the glycosuria (i.e., a single dose of 0.23 gm. per kg.). Doses of 40 gm. (0.47 gm. per kg.) caused an increase of 100 mg. in 2 hours. Doses of 60 gm. (0.69 gm. per kg.) caused increases of about 400 mg. in 2 hours. Reducing these figures for dog and man to the basis of 50 kg. of body weight and 24 hours, we find approximately:

	Period	Excretion Rate (gm. per 50 kg. per day)
Fasting (dog)	24 hrs.	0.3
Mixed diet (man)	24 hrs.	0.6
"Empty stomach" (man)	2 hrs.	0.6
Glucose feeding 11.5 gm. (man)	2 hrs.	0.6
Glucose feeding 23.0 gm. (man)	2 hrs.	1.3
Glucose feeding 34.5 gm. (man)	2 hrs.	3.4

While it is not certain that in these experiments the actual *rate* of glucose absorption rose uniformly as a straight line in proportion to the *quantities* of glucose given, it may have done so with these small to moderate doses. In any case the data *suggest* an exponential excretion curve rising at first very slowly from the horizontal and then bending rapidly upward the first glucose increment causing no acceleration of the excretion, the second causing a definite acceleration, the third equal increment causing 4 times the acceleration caused by the second.

In this connection it will be recalled that in fasting, although the

supply of food from exogenous sources ceases, the supply from the tissues increases and that in a normal individual weighing 50 kg., 50 to 100 gm. of glucose or more per day may be liberated in the body in the fasting catabolism of glycogen, protein and the glycerol of fat. In experiments of the above type the glucose administered passes first to the liver at the rate of absorption and probably emerges into the caval blood at a slower rate. The effect on the rate of excretion through the kidneys will naturally depend—other things being equal—on the rate at which glucose gains access to the systemic blood. It will be noted that in the above experiments doses of 34.5 gm. of glucose (per 50 kg.) caused the appearance in the urine of about 2.8 gm. of sugar in excess of that for the control period, i. e., about 8 per cent of the dose given was excreted (within 2 hours). This is in the general neighborhood of the percentage excretions observed by Sansum and Woodyatt when working with sustained intravenous injections of glucose at rates of 1 to 2 gm. per kg. hour. Probably then this dose of glucose by mouth led to the introduction of glucose into the systemic blood at about the above average rate. The curve of glucose excretion under higher rates of supply can not be followed far by the administration of larger doses of glucose by mouth because the upper limit for absorption rates is soon reached and the administration of more sugar than merely prolongs the duration of absorption without driving the rate above a certain maximum. However, when the rate of *intravenous* injection is accelerated, the rate of excretion rises absolutely and relatively. With injection rates of 4.5 to 5.4 gm. per kg. hour sustained for several hours, the excretion may rise in some dogs to 40 and 50 per cent of the quantity given and then remain virtually constant. Kleiner and Melzer, making single massive injections, within a brief time (rate possibly 15 to 20 grams per kg. hour or more) saw as much as 70 per cent of the dose excreted. Thus even in health it appears that there may be an absolute limit of tolerance beyond which all glucose given escapes utilization. We then have a curve consisting of a flat first portion which then bends rapidly upward and rises more and more steeply as the supply increases, somewhat after the manner of an exponential curve. A glycosuria might be considered as abnormal when with a known normal supply it is greater than with normal subjects under the same supply.

Any supply of glucose up to the limit that can be produced in a normal subject by feeding might be considered as not beyond the normal possibilities. Any glycosuria therefore greater than that which can be produced in health by the feeding of glucose will probably always be abnormal since it could only result (a) from a subnormal utilization; (b) an abnormal supply from endogenous sources; or, (c) an anomaly of excretion. But, of course, lower grades of glycosuria might also be abnormal if the supply rate were lower.

Diabetic Glycosuria

In cases of severe diabetes the entire curve of glucose excretion may be traced with supply rates rising from fasting levels to values no higher than may be produced easily by oral administrations. The curve then appears foreshortened. Miss H. Felscher has followed the total excretion of sugar in the urine of diabetics weighing 40 to 50 kg. from the time when as a result of diet limitations the urine became sugar "free," through periods in which the diet was gradually increased until a definitely abnormal glycosuria was produced. When the patients were in the non-diabetic state, the total sugar excretions (by the Benedict-Osterberg method) were usually between 300 and 600 mg. per day. As the diets rose gradually at 1 to 4 day intervals, the curves showed at first (a) no measurable rise at all, or (b) transient elevations with each diet addition followed by a return to the former level for the next day; or (c) progressive but slight upward trends from the beginning; until in any case a certain limit had been reached after which further additions caused sharp upward bends or critical breaks in the curves. Thus a certain severe case, weighing approximately 40 kg., showed an average excretion of well below 1000 mg. of sugar until the total glucose equivalent of the diet had mounted to 68 grams, when a further increment calculated as the equivalent of 4 grams of glucose caused the excretion to rise by 3.8 to 4.0 grams. Thus the severe diabetic appears to be capable of retaining glucose much as a normal individual when the supply is within the limits of his tolerance, but when the supply exceeds this limit, he begins at once to excrete an abnormal percentage of the excess. The transition from an almost complete retention to an almost complete excretion may be very abrupt and definable to within a few grams in sufficiently severe cases. Between this type of case and the normal there is every grade of transition, the difference between health and diabetes being one of degree. But even in health the curve may break sharply at a certain point.

Sugars Other Than Glucose in Diabetic Urine

All of the material that is called sugar in the normal urine is apparently not glucose, as stated above, but the absolute quantity of all sugars other than glucose in the average normal urine is so slight that in comparison with the quantities of glucose that may occur in diabetic urine, it may be neglected. Other sugars besides glucose may occur under exceptional conditions in quantities that are not negligible. Levulosuria, galactosuria, pentosuria, lactosuria, etc., are well known phenomena. They have been observed in non-diabetic individuals and they may doubtless

be found at times in association with diabetes when besides the true diabetes there are also the conditions responsible for these meliturias, e. g., the ingestion of pentoses in the food, intestinal flora that liberate pentoses from pentosans, diseases of the intestine and liver and other metabolic anomalies, but there is no convincing evidence in the literature that the occurrence of increased quantities of any sugar in the urine except glucose, is consistently associated with diabetes or that it has any direct relationship to this disease.

Mechanism of Glycosuria

Glucose is constantly being supplied to the tissues and constantly being utilized. The primary factors to consider are: (1) The rate of glucose supply, (2) the rate of glucose utilization. On their absolute values and the ratio of (1) to (2) will depend variations of the level of free glucose *in the body*. This level will also be influenced, theoretically, by a third factor, (3) the rate of glucose excretion. Thus glycosuria might theoretically be produced (a) by an abnormal increase of the rate of supply; (b) by an abnormal retardation of utilization; (c) by a lowered threshold of excretion provided that all other factors remained the same or provided they did not change in such a way as to affect one another. The character of the glycosuria will differ in certain respects depending on the mechanism involved. Increasing the rate of glucose supply in health increases the rate of utilization. As Allen has said, the more glucose is given the more is used. Within certain limits the rate of utilization appears to rise as fast or nearly as fast as the rate of supply. However, this ceases to be true when the rate of supply exceeds these limits. Utilization then lags and the lag grows progressively greater the more the supply is increased. Hence the higher the supply the greater the excretion absolutely and relatively. But with a normal power of utilization it is not possible by *feeding* experiments to produce anything approaching a quantitative excretion of all the glucose supplied in excess of certain limits, nor by subcutaneous injections nor by any method in which the supply rate is limited by the rate of absorption.

Diabetic Glycosuria.—The curves of glucose excretion obtainable in cases of severe stationary and uncomplicated diabetes are incompatible with any conception except that of a *failure to utilize* a normal percentage of the glucose supplied in excess of a certain limit. A heavy glycosuria due exclusively to an increased supply of glucose from endogenous sources could not occur without an increased utilization of glucose which would necessitate an increased metabolic rate and a high respiratory quotient. Lusk showed a 20 per cent increase of the metabolism in normal 8 to 9 kg. dogs following the administration of 50 grams of glucose by stomach. Even so the dose was insufficient to cause glycosuria in the ordinary

sense. That many cases of severe diabetes with marked glycosuria show low respiratory quotients and no increase of the basal metabolic rate is sufficiently established. Accordingly in diabetes there is no question but that we are dealing with glycosuria due primarily to an underconsumption of glucose. Although this is generally recognized, there are those who still maintain that this underconsumption is combined with an overproduction (Magnus-Levy).

Total Metabolism in Diabetes

In 1913 Magnus-Levy, reviewing the work of Leo(*b*), Stuve, Nehring and Schmoll Magnus-Levy, Mohr, Pettenkoffer, Voit, Ebstein(*f*), Johannson, Du Bois and Veeder, Weintraud, Laves, Benedict and Joslin(*a*), Falta, Grote and Staehelin, von Mering and Naunyn, concluded that mild cases of diabetes which are still capable of burning a certain amount of glucose do not differ essentially from the normal in respect of their total heat production and gaseous exchange, but that "In severe diabetes on the contrary, the oxygen consumption per kilogram is increased on the average about 20 per cent." Later development by Du Bois of his height weight charts for the calculation of surface area, the study of Allen and Du Bois on diabetes in the Russell Sage calorimeter and the criticism by Lusk of earlier interpretation of the data referred to, lead to conclusions that differ from those of Magnus-Levy in respect of the degree and frequency of elevations of the metabolism in severe diabetes. The differences in interpretation arise from differences in the method of calculating the body surface and in the manner of selection of non-diabetic controls. Benedict and Joslin interpreted their results to mean that in severe diabetes the average increase in metabolism was 10 per cent. They compared emaciated diabetics with emaciated non-diabetic controls. Applying the Du Bois height weight chart to the diabetics and controls of Benedict and Joslin (Severe Diabetes, Table 132) Lusk(*e*) finds:

	Per Cent
Average variation from normal of 20 controls	—8.6
Average variation from normal of 19 diabetics	+2.0

According to Lusk, "The increase in metabolism is therefore 2 per cent above the true normal, but 11 per cent above the normal controls (emaciated like the diabetics) selected by Benedict and Joslin." Allen and Du Bois on the same basis, summarizing the 26 cases of diabetes mellitus studied exactly by all investigations up to that time, found that 13 showed basal rates within the normal range (of + or — 10 per cent), 9 showed increases of 11 to 23 per cent, 4 showed metabolisms of 14 to 19 per cent below the normal. That in phlorhizin diabetes and pancreas diabetes

in animals the total heat production rises is agreed. Rubner saw an increase of 7 per cent, Lusk of 70 per cent in phlorhizin diabetes. Falta, Grote and Staehelin and Martin and Kramer saw increases of 42 per cent in pancreas diabetes. Lusk holds that Rubner was correct in attributing this to the specific dynamic action of the increased quantity of protein catabolized (Elements, p. 474).

It is quite certain that increased metabolic rates may be found in diabetic individuals; it is equally certain that an increased metabolic rate is neither an exclusive feature of diabetes nor a necessary accompaniment of the disease even when it is very severe. Excessive protein catabolism may occur even in uncomplicated cases of diabetes if the patient is permitted to become sufficiently impoverished in fat and excessive protein catabolism is capable of increasing the metabolic rate. An increased basal metabolic rate in a case of diabetes, if not due to high protein feeding, should lead to the suspicion of *fat starvation,* or *complications,* such as hyperthyroidism, infections or other factors that may lead to a "toxic" breakdown of protein. It is too early at the present time to dismiss this question as closed. With the general introduction of equipment for indirect calorimetry into the hospitals of this country as the result of the developments of simplified apparatus by F. G. Benedict, Boothby and Sandiford and others, it is certain that records of complete metabolism studies in diabetes will be multiplied in the near future. On my own service at the Presbyterian Hospital, using the Boothby-Sandiford development of the spirometer principle and the Du Bois height weight charts, a series of severe but uncomplicated cases have been studied all of which ran normal urinary nitrogens. The rates so far observed have varied between + 2 and — 18 per cent. From the Allen, Du Bois analysis, it would appear that acidosis is not incompatible with subnormal rates nor constantly present in cases that show increased rates.

Sources of Glucose Supply

Carbohydrates.—Carbohydrates, other than glucose, that are capable of complete utilization on the larger scale in the normal body appear to be completely convertible into glucose by the processes of digestion, intermediate metabolism, or both. At least this has been found to hold *virtually* true in the case of all carbohydrates that have been tested with sufficient care. Thus in cases of severe diabetes mellitus the feeding of starch and dextrin, the disaccharides fructose, maltose and lactose, the hexoses mannose, levulose and galactose, the trioses glyceric aldehyde and dihydroxy acetone and probably even the 2 carbon sugar glycollic aldehyde all lead to increased excretions of glucose in completely phlorhizinized dogs when the experiments have been beyond criticism. All of these form glycogen

in perfused livers. The conversion has been shown to be complete in the case of several carbohydrates which suggests that it would be possible to demonstrate the quantitative conversion of any of these carbohydrates that are capable of complete utilization in the normal body. The tetrose sugars, although utilizable, have been little used. The pentoses are not utilizable in health except in traces and are not glucose formers in diabetes. Glycogen yields in the end only glucose when hydrolyzed in the body or out of it. It is not only true that all utilizable carbohydrates are capable of conversion into glucose in the diabetic organism, but it is highly probable that in health they are so converted prior to oxidation, reduction or storage as glycogen (or analogues), that *conversion into glucose is the normal process of assimilation and a necessary prelude to storage or oxidation.* This is sometimes questioned but the support for the view is extensive. Glucose is the natural sugar of the blood. It is the one simple sugar that can be obtained by hydrolyzing glycogen. Efforts to produce a second kind of glycogen in the liver by feeding or by perfusing livers with levulose or other sugars (Cremer) have not been successful. There is only one kind of glycogen known and this is built up out of glucose. Glucose, as a rule, may be injected directly into a peripheral vein at the rate of 0.8 gm. per kg. hour in animals and man without abnormal glycosuria (Sansum & Woodyatt). For a 50 kg. man this is at a rate sufficient to supply 96 calories per kg. per day. On the other hand, lactose when injected by vein at the same rate reappears quantitatively in the urine. Levulose, reputed to be more easily utilizable than glucose in diabetes, produces definite levulosuria when injected at the rate of 0.1 to 0.15 gm. per kg. hour and possibly less. Even the triose glyceric aldehyde, which oxidizes so easily in the laboratory that it reduces Fehling's solution rapidly at room temperature, produces triosuria when injected intravenously at the low rate of 0.1 gm. per kg. hour. Galactose behaves in the same way. Yet all of these sugars are completely utilizable in large doses when given by mouth, in which case, of course, they pass to the liver first. They are all glycogen formers when perfused through livers and to form glycogen requires glucose. The liver is the prominent glycogen forming organ of the body and the prominent site of assimilation in general. All of these facts and others point strongly in the one direction *that the body burns (or otherwise utilizes) glucose and cannot burn directly any considerable quantity of any other carbohydrate.* In diabetes the power of assimilation is intact, but the attack on the glucose molecule fails. Hence glucose appears in the urine.

Protein.—The feeding of protein to a case of severe diabetes with glycosuria increases the glycosuria. The same holds in completely phlorhizinized dogs. As the experiments of Lusk have shown—both in phlorhizinized dogs and diabetes mellitus 100 gm. of protein fed may lead to the appearance of 3.65 grams of extra glucose for every gram of extra

nitrogen in the urine, and in the fasting phlorhizinized dog every gram of nitrogen derived from the body protein and excreted may be accompanied by 3.65 grams of glucose in the urine. This implies 58 grams of glucose from every 100 grams of protein catabolized. These figures are, of course, not absolute. Unless special precautions are taken, the animal is never strictly free of glycogen. All dogs do not show the same ratio nor any one ratio with perfect constancy. The ratio 2.8: 1 described by Minkowski in pancreas diabetes may also be seen in phlorhizin diabetes. Sansum and Woodyatt(*b*), working with completely phlorhizinized dogs that were deglycogenized by epinephrin usually obtained D: N ratios lower than 3.65 : 1. The fat also never disappears entirely from the body although it may approach the vanishing point when the experiment is sufficiently prolonged and no food is given. Glycerol is capable of quantitative conversion into glucose in the body and as long as fat is catabolizing, glycerol presumably must be liberated and be accounted for. In one of our experiments that continued 4½ days (after the ratio had settled), a fasting completely phlorhizinized and deglycogenized dog showed D : N ratios of 3.09, 3.04, 3.24 for 3 successive 6 hour periods on the last day. Ratios of 3.0, 3.04, 3.05 and 2.9 were encountered in the later stages of experiments with other dogs *even though earlier these same dogs had for 12 to 24 hours shown ratios between 3.5 and 3.8.* This belated falling of the ratio to a lower level suggests, at least, the possible derivation of glucose from other sources than protein during the earlier stages. The feeding of fat to phlorhizinized dogs was not observed by Lusk to increase glycosuria although glycerol is known to be convertible into its weight of glucose; but if the body had contained enough fat at the time of the fat feeding, the latter would not necessarily increase the actual catabolism of fat but would act simply as a replacement. Von Norden has pointed out in this connection that the feeding of fat need not of necessity increase the fat catabolism. It is not impossible that when the ratio of D : N is 3.65 : 1 other materials catabolizing constantly with the protein may liberate a fairly constant small quota of glucose (glycogen, glycerol of fat), which is then credited to the protein. However, the 3.65 ratio is one that is seen not only in phlorhizinized dog experiments. Almost the same ratio has been observed in certain cases of human diabetes. (Mosenthal.) It is a ratio better established than any single lower ratio that can be specified and it should be accepted until the claims of another are better substantiated.

Fat.—Fats when catabolized in the body must first be saponified to yield glycerol and higher fatty acids. Ringer reported that propionic acid was convertible into glucose and that certain other lower fatty acids with an odd number of carbon atoms were partly convertible but the ordinary higher fatty acids, all of which have an even number of carbon atoms, have not been found to be capable of forming sugar. Glycerol, as

is well known, is capable of complete conversion into glucose in phlorhizinized dogs and increases the glycosuria of human diabetes. The saponification of a fat such as triolein or tristearin yields 1 molecule of glycerol (mol. wt. 92) to 3 of oleic-acid (mol. wt. 284) or stearic acid (mol. wt. 256), a mixture in which 92 parts by weight are glycerol and 852 parts fatty acid, or 92 are glycerol and 768 fatty acid. A fat such as triolein would yield on saponification a mixture containing 9.7 per cent glycerol while tripalmitin will yield 10.7 per cent glycerol. The former type of fat predominating, we may calculate that 100 grams of fat catabolized in the body may liberate above 10 gm. of glycerol and so yield about 10 grams of glucose in the body.

Other substances besides carbohydrate, protein and fat that are capable of yielding glucose in the body include lactic acid, but the above are the chief sources of glucose supply under natural conditions.

Deductions.—If we assume in a given case of diabetes that all of the glucose that enters the metabolic stream is derived from carbohydrate, protein and fat and designate these as C, P and F respectively; and if we designate the total quantity of glucose liberated in the body from all sources (endogenous and exogenous) as G, then approximately:

$$G = C + .58\,P + .1\,F$$

In the clinical literature of diabetes much is written of "carbohydrate" tolerance. This frequently means the quantity of *utilizable carbohydrate that can be included in the diet* without overtaxing the glucose tolerance. Other glucose forming elements in the diet and the endogenous sources of glucose supply are commonly neglected. A normal subject. S. A. B., body weight 59 kg., studied by F. G. Benedict(*c*) showed on the fourth day of fasting a catabolism of carbohydrate (glycogen) 25.17 gm., protein, 69.78 gm., fat, 144.72 gm. Taking the carbohydrate plus 58 per cent of the protein plus 10 per cent of the fat we find that on that day 80 gm., or about 1.36 gm. per kg., of glucose could have been liberated in the body. On the first day of fasting the same subject had catabolized carbohydrate 64.9, protein 73.44, fat 126.4 gm. capable of yielding 120 grams of glucose or 2.0 gm. per kg. On diets that entail undernutrition and especially when dealing with individuals that are impoverished in fat and must therefore catabolize much protein, the gross errors that may arise from calculating the glucose supply from the diet alone are apparent.

Cause of Underconsumption of Glucose in Diabetes

In 1788, Cawley reported atrophy and stone of the pancreas in a case of diabetes. The coincidence of diabetic symptoms and lesions of the

pancreas was further studied by Bright, Lloyd and Elliotson (1833). Bouchardat(*a*) at first definitely formulated the belief that pancreatic disease was the cause of diabetes mellitus. Von Mering and Minkowski (1889) proved that *complete* pancreatectomy leads invariably to the development of a severe diabetes.

This applies not only to dogs but to cats, rabbits, pigs (Minkowski) tortoises, frogs, eels and other animals.

The glycosuria begins soon after the operation and increases in intensity. "It persists in spite of a non-carbohydrate diet long after the glycogen reservoirs in the liver and muscles have become greatly impoverished (to 0.1-0.2 per cent in the liver), but like the human disease, it usually ceases during a fast or may disappear just before death." [2]

The glycosuria may be accompanied by an excretion of the acetone bodies,—acetone, acetoacetic and β-hydroxybutyric acids. In fact, the metabolic changes secondary to this operation closely parallel those found in the human disease, with certain differences which perhaps are ascribable to species or to the fact that in the experimental diabetes digestion is altered by absence of the pancreatic juice, etc. The following points have become firmly established by frequent repetition. (1) *Complete* removal of the pancreas causes a true diabetes (as above). (2) Ligation or obliteration of the duct (or ducts) of Wirsung, no matter how scrupulously carried out, has no such effect. (3) If about 1/16 to 1/10 of the pancreas (Minkowski) with its arterial supply be separated from the rest of the gland, this portion may be implanted extraperitoneally at a distance from the original site. No diabetes results from this operation, or at most only a transient glycosuria. Now if the main body of the pancreas be fully extirpated with ducts, nerves and blood-vessels, still only a transient glycosuria or none at all develops. At this stage all possible damage to nerves and external secretion would seem to have been inflicted and proved incapable of causing diabetes. (4) In the course of weeks the *rest* atrophies (Sandmeyer's experiment), and then a persistent glycosuria supervenes; or the encapsulated fragment may be extirpated, in which case within a few hours a severe diabetes ensues. (5) There is no other organ in the body extirpation of which has any similar effect, nor (except for phlorhizinization) is there any known means of experimentally producing a *true* diabetes without injury to the pancreas. (6) No toxic substance derived from the body of diabetic individuals, man or animal, has been found which is capable of causing diabetes in a second animal. *These facts lead to the conclusion (reached by Minkowski) that pancreatic tissue provides something separate from the pancreatic juice (internal secretion of the pancreas), the lack of which is responsible for the symptoms of diabetes.*

[2] The last statement, confirmed by personal observation, appears in a chapter on Diabetes by Woodyatt in Wells' "Chemical Pathology," 2d Ed., 1914.

Cause of the Impaired Glucose Utilization in Diabetes

The relationship between the diabetic defect and the pancreas appears to be definitely established.

Islet Theory: Morphologically the pancreas may be regarded as stroma ducts, acini and islands of Langerhans. It has been proposed, notably by Opie in this country, that the antidiabetic internal secretion of the pancreas is elaborated by islet cells. This view finds support in the following facts: (1) In diabetes mellitus the islets are frequently found in a state of hydropic or hyaline degeneration, while the remaining organ may appear normal. (2) Cancer, pancreatitis and the experimental injection of caustics into the ducts very frequently spare the islets and fail to cause diabetes. (3) It is claimed that in pancreatic grafts, such as described above, islet cells predominate, while acinus cells and ducts disappear. Grafts of this kind consist of much connective tissue, generally more or less infiltrated with round cells, and collections of epithelium. Concerning the latter, remains of ducts and acini are usually present in some proportion and there are also epithelial cell masses regarded as islets on morphological grounds. Differences of opinion still exist as to the relative proportion of the different epithelial elements. Lombroso, whose exhaustive monograph reviews the literature to 1910, concludes that the internal function of the pancreas is not monopolized by islet cells. Bensley developed intravital staining methods which, for the first time, made possible the sure differentiation of the islet cells from duct or acinus epithelium without reference to form or arrangement and appears to have proved that these cells are regenerated from duct epithelium. He also showed the great normal variations in size and number of islets in different individuals (guinea-pigs). His study explains certain of the discrepancies which occur in the literature, especially in the estimation of the quantity of islet tissue in pancreatic rests, grafts, etc. Allen has reported that when proper sized fragments of pancreas in connection with the ducts are left in situ, and the remainder of the gland is removed, the subsequent development of severe diabetes may be coincident with disappearance of islet tissue while acinus cells and ducts are unaffected. This operation, according to Allen, is eminently satisfactory for producing experimental diabetes without infection and without loss of the external secretions.

In completely depancreatized dogs Minkowski saw quantitative excretions of administered carbohydrates and D : N ratios of 2.8 to 1.

The lower ratios observed in pancreas diabetes as compared with phloridzin diabetes and some cases of diabetes mellitus might perhaps be interpreted as due to differences in the proportion of fat catabolized.

The Nature of the Internal Secretion of the Pancreas

Although the indirect evidence of a pancreatic hormone in health whose absence or presence in deficient quantity or potency is responsible for diabetes is of the most concrete sort, we have no knowledge of the hormone itself. We know it only as something missing in diabetes and the endocrin function of the pancreas so far as we know anything about it at all, is simply that which is responsible for what fails to occur in the diabetic metabolism. The defect of the metabolism which characterizes diabetes is a single specific defect—a failure on the part of the body to oxidize, reduce, polymerize, or otherwise chemically alter a normal percentage of the glucose supplied to it in excess of a certain quantity. In the most complete cases of diabetes glucose molecules enter into the chemical reactions of the body, figuratively speaking, like so many glass beads. Liberated in the body or introduced into it from without, they rattle about until they fall out through the kidneys. This defect is present in some degree in every case of diabetes. When present, we are justified in speaking of diabetes. When absent, we may not speak of diabetes. There is no other known defect of the metabolism of which this can be said. Accordingly, *the endocrin function of the pancreas, so far as known, is a single highly selective function having to do with the chemical activation or dissociation of a single specific sugar glucose and nothing else.*

Possible Mechanism of Its Action.—A parallel to the behavior of the normal and diabetic body which is suggested by Van Slyke's study of the enzyme urease is probably more than a mere scheme of illustration. Let a narrow dialyzing bell be partly filled with water and immersed in a beaker of water. Add to the water in the bell, which is closed at the bottom by a dialyzing membrane, a suitable quantity of urease. Add to the enzyme containing solution a small quantity of urea. Splitting begins and proceeds at a certain velocity. The addition of more urea accelerates the reaction and so on with successive additions until finally a point is reached at which further additions accelerate it no more. All of the enzyme present is then engaged in maximum activity. Further additions of urea now increase the quantity and concentration of urea in the dialyzer more rapidly than earlier additions. When this point is reached the diffusion of unchanged urea through the membrane which has been rising but little should rapidly accelerate. If in such an apparatus one were to plot the curve of urea diffusion into the beaker, one would obtain a curve resembling that of glucose excretion by the body under an increasing glucose supply. If there were much urease present, the curve would rise more gradually and much urea would be required to reach the limit of acceleration of splitting. With little enzyme present, the curve would be short

and break upward abruptly. If the dialyzer contained a *glucase* instead of urease and if glucose were added, the analogy would be complete.

The pancreas is a gland innervated from the celiac plexus with vagus and sympathetic fibers. If its function is to dispose glucose, more glucose means more work to be done and more glucolytic secretion to be elaborated. Glucose itself might be conceived as directly or indirectly stimulating this nerve gland apparatus. Given an imperfect organ and an overburden of glucose and fatigue or permanent injury might presumably result. Relief from the overburden with rest for the apparatus would favor recuperation to a degree. What originally weakens the apparatus in diabetes mellitus?

The feeding of pancreas—fresh or dried—does not cure diabetes as thyroid gland cures cretinism. The pancreatic hormone does not contain iodin like that of the thyroid to indicate by a violet color whether it is present or absent in an hydrolysis fraction. It would not be expected to produce any immediately recognizable effect if injected into a normal animal already containing it in excess. Unless Kleiner with a pancreas emulsion has demonstrated an increased utilization of sugar, post mortem in depancreatized dogs, no definite results have been attained with pancreas preparations as yet.

Acidosis

The anomaly of the metabolism in which abnormal quantities of acetone, acetoacetic and β-hydroxybutyric acids appear in the tissues, blood and urine, is not due directly to any impairment of the endocrin function of the pancreas. It is a secondary effect in the nature of a disturbed metabolic balance resulting from the withdrawal of oxidizing glucose. This anomaly is not peculiar to diabetes nor constantly associated with it. It occurs in other diseases. It may be made to appear in a normal subject by starvation or a diet containing too low a proportion of carbohydrate and too high a proportion of fat, and when this is done it may be made to disappear again simply by the addition of more carbohydrate to the diet. It appears to be *the immediate result of the oxidation of certain fatty acids in the absence of a sufficient proportion of "oxidizing" (dissociated) glucose.*

It would seem probable that for any given individual at any given time there is *a definite ratio between the quantity of glucose oxidizing in the body and the maximum quantity of ketogenic acids that can be oxidized in the same time without the appearance of abnormal amounts of the acetone bodies.* In other words, *the quantity of oxidizing glucose fixes an upper limit to the quantity of ketogenic acid that can be completely oxidized at the same time.* As to the absolute magnitude of this ratio and the degrees of its variation in different individuals in health and disease, final state-

ments can not now be made. In December, 1910, on the basis of chemical studies by Ciamician and Silber, and test tube experiments with acetoacetic acid, I suggested a certain type of reaction as the basis of "Antiketogenesis" in which one molecule of acetoacetic acid would react with one molecule of an alcohol or glucose. Zeller, working with normal individuals on ample diets consisting of carbohydrate and fat with very low protein contents, shifted the proportions of fat and carbohydrate without changing the total calories and saw acetone appear when the ratio of carbohydrate calories fell below 10 per cent of the total; that is, when the ratio of fat to carbohydrate *in the diet* in grams was about 4 to 1. Recalculating Zeller's experiments, Lusk estimated the relative quantities of sugar and higher fatty acid that might have been oxidizing together in the body. Allowing for the formation of sugar from the glycerol of the fat, and the glucose from the protein catabolized and for some glucose from glycogen, but not for ketogenic amino-acids from protein, Lusk suggested that possibly one triose molecule was necessary for the complete oxidation of 1 of higher fatty acid that is, 1 molecule of glucose to 2 of higher fatty acid. Recently, Palmer has repeated experiments of the Zeller type in diabetics and obtained results that appear to be harmonious. P. A. Shaffer(*c*) has worked with test tube experiments and with diabetic individuals in which he conducted metabolism studies, including observations of the respiratory quotient at the time acetone first appeared. Shaffer calculated the ketogenic acids of protein on the basis of the quantities of leucin, tyrosin and phenyl alanin found in 100 grams of ox muscle protein by Osborn, assuming that each molecule of these known acetone formers may yield 1 molecule of acetoacetic acid or its equivalent. As a result of his work, Shaffer suggests that one molecule of glucose is necessary for the complete oxidation of 1 molecule of acetoacetic acid or 1 molecule of any higher fatty or amino-acid that yields 1 molecule of acetoacetic acid (or equivalent).

The molecular weight of glucose being 180, of oleic acid 284, of palmitic acid 256 and the average of the two acids 270, the ratio found by Shaffer, if expressed in grams, would be 1.57 or 1.42, average 1.5 grams higher fatty acid to 1 gram glucose. Working with diabetic patients on maintenance diets under conditions that made it probable that the proportion of foodstuffs in the diets corresponded fairly with those catabolized in the body, and estimating the glucose and fatty acid as hereinafter indicated, Woodyatt also observed at the time acetone appeared, ratios varying about 1.5 with considerable frequency. Accordingly even though it may prove necessary to revise the figure as data accumulate, it would seem that for clinical purposes and for the time being one would make no gross error in assuming that as a general rule the ratio of higher fatty acids to glucose which, if exceeded *for a sufficient length of time,* will lead to acidosis is over and under 1.5 to 1 (in grams). Higher ratios without acetonuria are not rare but, when observed, the question arises as

to the quantity of fat actually catabolized. Of course especially in the young lower ratios will also be seen.

These figures apply in the case of the body taken as a whole. The formation of acetone bodies is a process which appears to be confined very largely to the liver. Recently Witzemann has discussed the peculiar proclivity of the liver to form acetone from butyric acid in relationship with the ammonia metabolism of the liver. Ammonia was the base that Dakin used in his oxidation of butyric acid with hydrogen peroxid when he first demonstrated the possibility of producing acetone bodies from the oxidation of fatty acids in the test tube. Witzemann shows that the power of ammonium to induce acetone formation is not shared in equal degree by alkalis in general, but is a specific property of ammonia itself, and that even the sodium and potassium salts of butyric acid when oxidized in the presence of ammonia, yield more acetone than in the absence of ammonia. Possibly that interaction between oxidizing glucose and oxidizing fatty acids that destroys acetoacetic acid or prevents its accumulation in abnormal quantities ("ketolysis," "antiketogenesis") also occurs chiefly in the liver, in which case the ratio above discussed may be particularly affected by variations in the size or condition of the liver. Migrainics, epileptics and others with disordered hepatic functions would not be expected to behave in this respect exactly as normals.

For clinical purposes, it may be calculated that 100 grams of mixed fat in the diet, if completely absorbed and catabolized, will introduce into the metabolism about 90 grams of higher fatty acid. Protein of the diet, or tissues, is resolved into amino-acids and in so far as these are absorbed and catabolized, they must be deaminized (and presumably at the same time oxidized) to yield oxy or hydroxy acids. Of these a part is convertible into glucose, another part into β-hydroxybutyric and acetoacetic acids, while a third small fraction is destroyed in as yet unknown ways. 100 grams of protein introduce a certain quantity of products which are the equivalent of products of the higher fatty acid catabolism in that they are capable of yielding β-hydroxy and acetoacetic acids. The exact quantity of these substances formed in the catabolism of 100 grams of protein can be only roughly estimated. The amino-acids that are certainly known to yield acetone bodies are leucin, tyrosin and phenyl alanin. If we take the quantities of these amino acids found in 100 gm. of ox muscle protein by Osborne and Mendel, as Shaffer has also done and convert the weights given into gram molecules, we obtain 0.16 gram molecules of these ketogenic amino acids (per 100 gm. protein). If we assume that each of these molecules of amino-acid is capable of yielding 1 molecule of acetoacetic (or β-hydroxybutyric acid) and accept the view that 1 molecule of a higher fatty acid such as oleic or palmitic acid also yields 1 molecule of acetoacetic (or β-hydroxybutyric) acid in the course of its catabolism, then the 0.16 gram molecule of ketogenic amino-acids would be equivalent

in respect of its ability to form acetoacetic acid to 0.16 gram molecule of higher fatty acid. If the acid were oleic (molecular weight 284) this would represent 45.44 grams. This affords a tentative figure that serves a practical purpose even though it be subject to correction.

The relationship may be expressed in the form of an equation. If F A is the total quantity of higher fatty acid introduced into the metabolism (plus ketogenic amino-acids expressed in terms of higher fatty acid) and if P = protein; and F = fat (neutral), then

$$(1)\quad \mathrm{F\,A} = .44\,\mathrm{P} + .9\,\mathrm{F}$$

We have previously noted that the total glucose derivable from a given food supply may be expressed approximately as

$$(2)\quad \mathrm{G} = \mathrm{C} + .58\,\mathrm{P} + .1\,\mathrm{F}.$$

If the ratio of F A : G, which, if exceeded, leads to acetonuria, is in a given case 1.5 : 1, then when $\frac{\mathrm{F\,A}}{\mathrm{G}} = 1.5$ we derive from (1) and (2) the equation $\mathrm{F} = 2\,\mathrm{C} + .57\,\mathrm{P}$, which for clinical purposes and convenience in mental calculations may be stated simply as

$$(3)\quad \mathrm{F} = 2\,\mathrm{C} + \frac{\mathrm{P}}{2}$$

Dietetic Management of Diabetes

In the dietetic management of diabetes we are engaged in the effort to correlate symptoms and signs shown by the patient with the kinds and quantities of food that he consumes. The success of treatment, the average of results in all types of cases, depends on the truth of one's concept of the relationships between symptoms or signs and the food supply. During the last few years the average of results obtained in the diabetic management of diabetes has been much improved through the work of Allen and Joslin and the system that they have developed is in some respects more logical and less empirical than any that we have had heretofore. Yet the literature of the subject is still confused by a lack of unanimity among all writers as to the best manner of handling all cases. In a recent monograph, Falta(*e*) has again told the merits of his "cereal cure" (*Mehlfrüchte Kur*), and endorsed methods of management that differ materially from that which has found so much favor in this country. Newburgh and Marsh, of Ann Arbor, failing to achieve practical results by their application of the principles of "total dietary restriction" resort to low protein, high fat diets with striking immediate results in the management of seventy-four cases. In the past, good results were obtained in some cases by old fashioned "rigid" diets. The remarkable improvements that have sometimes been seen with the institution of a Donkin

"milk cure," a von Duering "rice cure," a Mossé "potato cure," a von Norden "oatmeal cure," or any one of several analogous procedures can not be denied and have never been fully explained to the extent that one may predict with certainty just when one of these empirical procedures will, and when it will not, produce a result better than that attainable by a more systematic method.

Discrepancies in the clinical literature of diabetes arise from three main sources:

(1) Confusion in the minds of writers as to the exact nature of the anomaly of the metabolism which characterizes diabetes with a resulting lack of understanding of the rationale of dietetic management.

(2) A general tendency to think of the food supply of the body too exclusively in terms of the diet to the neglect of endogenous factors, and

(3) The custom of thinking of the food supply simply as so much carbohydrate, protein and fat, and as so many calories without further analysis.

1. Rationale of Dietetic Management.—It would follow from the preceding discussion that the rationale of dietetic management in diabetes is to bring *the quantity of glucose entering the metabolism from all sources below the quantity that can be utilized without abnormal waste; and to adjust the supply of ketogenic acids in relationship to the quantity of glucose* so that in the mixture of foodstuffs oxidizing in the body, the ratio of the ketogenic acids to glucose shall not exceed limits compatible with freedom from ketonuria. When as, and if, under these conditions of relative rest for the pancreas, the glucose-using function improves, then the food supply may be increased gradually in so far as this can be done without disturbing the above relations.

2. Endogenous Factors of Food Supply.—Normal men during a fast on light exertion have been observed to produce 29 to 30 calories per kg. of body weight daily. For a 50 kg. man, this implies 1500 calories per day. During the first 4 days of a fast Cetti produced on the average 29 calories per kg. for a total of 1618 calories per day, and catabolized 85.88 gm. of protein for 329.8 calories and *136.72 gm. of fat for the remaining 1288 calories.*[3] In a case studied by F. G. Benedict,[4] on the second day of fasting there were produced 1768 calories, or 29.9 calories per kg., and the individual was estimated to have catabolized 7.47 grams of protein, *147.6 grams of fat* and 23.1 grams of glycogen. Thus a well nourished normal man weighing 50 kg., who during a fast produces 1500 calories per day may actually catabolize in the neighborhood of 75 gm. of protein, 125 grams of fat, and a little carbohydrate from glycogen. These are well known facts repeated simply to emphasize the magnitude of the food supply from the tissues in fasting and to point out in particular

[3] Citation from Lusk, Elements of the Science of Nutrition, 3rd, pp. 86-89 (1917).
[4] The Influence of Inanition on Metabolism, p. 184, Table 128 (1907).

that in fasting, *over 100 grams of fat may be thrown into the metabolic stream and catabolized daily.*. It has further been shown that the amount of fat in the fasting organism materially effects the amount of protein burned. In a critical review of the literature of the subject Lusk has said: *"Where there was much fat present, little protein was consumed; where there was little fat, much protein burned; and where there was no fat, protein alone yielded the energy for life.* In a normal individual the ingestion of fat will not prevent the death of the organism because there is a continual loss of tissue protein from the body, which finally weakens some vital organ to such an extent that death takes place." *But the ingestion of fat may spare tissue fat and thus prevent the protein loss from becoming abnormally great.* It may be said that the ingestion of fat spares the individual any such protein loss as will occur if the tissue fat is allowed to become too much depleted. In this sense the ingestion of fat by an emaciated individual spares protein for that individual. In other words fat always spares protein but we do not realize it until the sparing effect is removed. Voit found in a fasting animal that the ingestion of suitable amounts of fat scarcely influenced the protein metabolism. To one dog "which in starvation burned 96 grams of fat, Voit gave 100 grams of fat with the result that it burned 97 grams. *The fat ingested simply burned instead of the body fat, but the total amount of protein and fat burned remained the same."* (Lusk.)

Now, if a certain diabetic patient during a fast reacts essentially as a non-diabetic individual in the same state of nutrition; and if he weighs 50 kg., produces 1250 to 1500 calories, and in doing so actually mobilizes and burns 100 to 120 or more grams of fat, the ingestion of *an equal quantity* of fat should leave his metabolism in the same state as before. The supply of fat would come at one time from the tissues, at another from the diet, but the quantity thrown into metabolism, the quantity presenting itself for disposition in the cells, and the quantity of internal secretion or enzyme that the cells would have to provide would be the same in both cases. *The practice of placing a patient on a diet of greens containing not over 18 gm. carbohydrate, 6 gm. of protein and no fat, or on complete fasting for the purpose of desugarization, would not seem necessary or rational in the light of these facts.* In such cases fasting would be rational if it would improve the general condition. But for diabetes itself, and particularly for diabetes associated with undernutrition, why for the purpose of desugarization should the patient be compelled to draw from his tissues the fat that he might draw from a diet, especially if in drawing from his tissues he lowers his fat reserves to the extent that he increases his protein losses? The striking results that have been obtained recently by Newburgh and Marsh with high fat, low protein, diets bear significantly on this point. The practice of starving, or virtually starving, a patient in order to render his urine sugar "free" and then of building up the diet first with carbo-

hydrate and then with protein with a particular avoidance of fat as urged by Joslin, would appear to be based on the supposition that if fat were administered it would increase the catabolism of fat. But this would be in disregard of the endogenous food supply. As the diet falls the endogenous supply rises to take its place, and vice versa. The lower the diet, the less its significance in calculating the food supply from all sources. It is possible to maintain the normal body with a diet that contains but 10 per cent more calories than are produced in fasting, and the difference in metabolism of a man when receiving no diet and when receiving a 1500 calorie diet has been greatly overestimated by those who as a routine employ fasting in the treatment of diabetes.

3. Dealing with the Food Supply in Terms of Carbohydrate, Protein and Fat.—Carbohydrate, protein and fat are, as such, three separate and distinct substances, no one of which can be expressed quantitatively in terms of another and if we speak of food supplies or diets as made up of so much carbohydrate, so much protein and so much fat, we simply name them in terms of three variables. Thus each particular combination or diet becomes a specific, and having learned by experience how one of them will affect a certain patient, we have no means of knowing exactly how a second dissimilar combination will affect the same patient, much less another, except by trial and experience. The number of possible combinations of three variables is infinite and the number of practical food combinations, no two of which will differ by less than 5 grams of one ingredient, or by less than 50 calories, runs into the thousands. Accordingly if we attempt to correlate symptoms and signs shown by the patient with the diet and follow the usual system of dealing with diets simply in terms of carbohydrate, protein and fat, without attempting to resolve them into simpler terms, it will be necessary to establish by experiment the effects of each diet combination in every type of case. It would seem tedious and hopeless to proceed by this inductive method. A further objection to this method, and a clear advantage in using another, lies in the fact that protein, carbohydrate and fat as such are not the substances that present themselves for the final oxidative attack in the body which results in the liberation of energy. These substances are resolved by the processes of digestion and intermediary metabolism into simpler substances before they can be burned in the tissues. It is not starch in the bowel nor glycogen in the liver and muscles that taxes the endocrin function of the pancreas, but the glucose into which these carbohydrates are resolved. Protein of the diet ceases to be protein and becomes a mixture of amino acids before it can be absorbed from the bowel and these undergo deaminations, etc., prior to actual oxidation. Neutral fats may be absorbed in part as such and are frequently deposited in the tissues as such, but before they can be oxidized and used as sources of energy, they must presumably be saponified into glycerol and higher fatty acids. Thus, as a matter of

fact, carbohydrate, protein and fat are not the actual foodstuffs with which we are dealing when it comes to the final metabolic processes. In the management of the diabetic food supply it is simpler to think in terms of the chemical metabolism. Falta devised a formula in which he added the carbohydrate of the diet to the urinary nitrogen times 2.8, or (following Lusk's suggestion, 3.65) to show the total quantity of glucose entering the body on a given diet from carbohydrate and protein. Then subtracting from this the quantity of glucose excreted in the urine, he obtained a figure for the quantity of glucose actually utilized. The quantity excreted divided by the total quantity supplied gives a fraction which, multiplied by 100, was Falta's diabetic quotient 100 meaning a complete diabetes. The latter has a limited value. The absolute quantity utilized is of more interest. The principle is important and can be further developed as already shown.

4. Discussion of Hypothetical Diets.—In this connection consider four hypothetical diets, I, II, III, and IV, and analyze them from the viewpoint of their possible effects on a certain diabetic patient weighing 50 kg. Let it be assumed that each diet is completely digested, absorbed and catabolized, and that each is sufficient to cover the maintenance requirements of the body, so that in discussing them one may waive endogenous factors.

TABLE II

	I	II	III	IV
Carbohydrates	10	77	60	51
Protein	84	108	91	135
Fat	150	30	85	70

Looking at these diets simply as so many different combinations of carbohydrate, protein and fat, and going no further, they appear to be quite dissimilar. Diet No. I is a fair example of the old-fashioned "rigid" diet with almost no carbohydrate and the protein at 3 grams per kg. of body weight. Diet No. II is a high carbohydrate, low protein diet. It is the kind of a combination that might possibly be given in a "rice cure," an "oatmeal cure," or a "cereal cure." This diet would permit the patient to enjoy 385 grams, almost a pint, of boiled rice or other cereal; or, he could have 154 grams of white bread. Diet III appears to be intermediate between I and II in all respects. It contains less carbohydrate than II but more than I, and the fat is less than in II and more than in I. It contains nothing that is not contained in higher quantities by one of the other diets. Diet No. IV resembles II but might be suspected of having a higher caloric value because of its fat. Diets I, II, and III each represent 1400 calories, while IV shows about 1700 calories. If in each diet we estimate G, we find that I and II are alike in that each is capable of introducing about 105 grams of glucose into the metabolism. The patient capable of utilizing 105 to 110 grams of glucose per day might tolerate either

of these diets. For diet III G is 118. This apparently innocent intermediate isocaloric diet will cause glycosuria in a patient who is capable of utilizing only 105 to 110 grams. Diet IV, with 300 more calories than any of the others, has the same glucose equivalent as I and II and would probably be borne as well as either. The question arises in respect of diet IV as to whether the high fat is permissible or in any sense objectionable. Estimating the higher fatty acid value of this diet by means of the formula, it appears that F A is 152.3. G being 105, the ratio $\frac{F\ A}{G}$ is 1.45. *As a general rule, acetone does not appear in the urine of uncomplicated cases of diabetes, or remain permanently, if present, until the ratio reaches or exceeds 1.5 : 1* provided that the diet is completely utilized and sufficient for maintenance so that endogenous factors of food supply do not complicate the calculation. Accordingly the quantity and proportion of fat in diet IV are not necessarily too high for complete utilization in the normal manner.

5. Estimation of "Optimal" Caloric Diets.—If C = carbohydrate, P = protein, F = fat, G = glucose and F A = higher fatty acids (plus other ketogenic acids expressed in terms of higher fatty acid) in grams, the quantity of glucose which any given food supply will introduce into the metabolism is expressed by: (1) $G = C + .58P + .1\ F$ and the quantity of higher fatty acids (and equivalents) may be expressed as: (2) $F\ A = .44\ P + .9\ F$. When the ratio $\frac{F\ A}{G}$ exceeds a certain value for a given case, ketonuria develops. Assuming for a given case that the ratio is actually found in the neighborhood of 1.5, then $\frac{.44\ P + .9\ F}{C + .58\ P + .1\ F} = 1.5$ when the ratio of fatty acids to glucose is as high as it may be without ketonuria. Simplifying, $F = 2\ C + .57\ P$, or simply (3) $F = 2\ C + \frac{P.}{2}$ If it is assumed that the ratio F A : G shall not be allowed to exceed 1.5, and that the relationships expressed in equations (1) and (2) are as given, then to estimate the optimal food combination or diet one may use equations (1) and (3). Given the quantity of glucose that the patient can utilize completely (which must be found from his behavior on some known diet), assign this value to G in equation (1). Thus if 100 gm. is the highest quantity of glucose derived from all sources that the patient can utilize completely at a given time, 100 grams $= C + .58\ P + .1\ F$. In order to secure the maximal number of calories, the diet must clearly contain every possible gram of fat (at 9 calories per gram) that the value of G and the relations expressed in (1) and (3) will permit and consequently the lowest possible carbohydrate protein fraction (at 4 calories per gram). Also as between carbohydrate

and protein, the protein must be as low as possible and the carbohydrate as high as possible for 1 gram of carbohydrate yielding 1 gram of glucose and 4 calories provides for the normal oxidation of 1.5 grams of higher fatty acid. On the other hand, 1 gm. of protein having the same caloric value as carbohydrate yields less glucose to support fat combustion, and in addition yields acetone bodies itself. If the body weight of the patient be 50 kg. and if 1 gm. of protein per kg. is selected as a conservative minimum, then P becomes 50 grams and $F = 2\ C + \frac{P}{2}$ becomes $F = 2\ C + 25$. From the above G = 100 gm. Now the glucose yielded by the 50 gm. of protein will be .58 × 50, or 29 grams, leaving 100 — 29 or 71 gm. to be distributed between carbohydrate and fat. In other words, $C + .1\ F = 71$, or $F = 170 - 10\ C$. But also, $F = 2\ C + 25$, so $2\ C + 25 = 710 - 10\ C$, solving which: C = 57 gm. (57.08). Substituting this value for C in $F = 2\ C + 25$ we find F = 139 grams (139.16). Then the optimal food combination that will fulfill the conditions and relations specified is:

Carbohydrate =	57 grams
Protein	50 grams
Fat	139 grams
Calories	1680

Proving this diet it will be found that G = 57.08 + (.58 × 50) plus (.1 × 139.1) = 99.98 as called for. Also F A = (.44 × 50) plus (.9 × 139.1) = 147.19. And $\frac{F\ A}{G} = 1.47$. The small error arises from the dropping of decimals in equation (3).

It is apparent that any addition of any foodstuff to this diet would make G>100. If, on the other hand, one added more fat, say 10 grams, and subtracted 1 gm. of carbohydrate, G would remain 100 and the calories would be increased by 86, but this would make $\frac{F\ A}{G} > 1.5$. The effect of changing the protein can be seen by comparing the caloric value of a series of optimal food combinations with the protein rising from 0 to 2.0 gm. per kg. (See Table III.)

(6) Remarks.—Cases are not infrequently seen which show ketonuria when the ratio of F A to G in the diet is much lower than 1.5. This is true especially in some children and some migrainic adults. Also it will frequently be found possible to administer diets in which the diet ratio is 2.0, 2.5 or 3.0 and even higher without the appearance of ketonuria for long periods of time. This would appear to be especially true of emaciated individuals. Analysis of the quantities of carbohydrate, protein and fat actually catabolizing in the latter cases has in several instances revealed

TABLE III

Showing optimal food combinations when G = 100 gm. (in the equation G = C + .58 P + .1F); when F A = .46 P + .9 F; when F A : G = 1.5; and when the protein is 0, 25, 50, 75 and 100 gm. (i. e., 0; 0.5; 1.0; 1.5; and 2.0 gm. per kg., if the body weight is 50 kg.).

P.	C.	F.	Calories	Difference in Calories
(1)* 0.0	83.3	166.7	1833.3	76.25 (2)—(1)
(2) 25.0	70.2	152.9	1757.1	76.25 (3)—(2)
(3) 50.0	57.1	139.2	1680.8	76.25 (4)—(3)
(4) 75.0	44.0	125.4	1604.6	76.25 (5)—(4)
(5) 100.0	30.8	111.7	1528.3	

* No. 1 is hypothetical and could only be considered as the non-protein fraction of a larger combination.

For each gram of glucose that can be utilized in the body there are some 18 calories in the "optimal" food combination. Each gram of protein in the food supply is seen to subtract 3 calories from the optimal. For rapid mental calculation knowing that a patient can actually utilize a certain number of grams of glucose, take the number times 17 as the approximate number of calories that he will probably be capable of using without glycosuria or acetonuria.

the storage of part of the fat ingested. In assigning values to terms of the equation, it will be found generally preferable—whenever possible—to measure the material actually catabolized. Thus for the term .58 P the total urinary N × 3.65 will be preferred to the protein of the diet × .58. An estimation of the total calories produced minus the calories derivable from the protein catabolized may give a truer idea of the fat catabolized than will be obtained from the dietary figures alone, and so on. Some of the above discrepancies disappear when this is done, but not all. The equation illustrates a method of thought rather than a set of fixed rules. Some cases which tolerate dietary ratios higher than 1.5 for considerable lengths of time without ketonuria may later show ketonuria on the same diet and it is well not to permit patients to pass from close observation with ratios exceeding this figure even if it seems advantageous or necessary to employ them at times. Possibly the ratio of 1.5 is too high for the long run in some cases.

The practice of withholding all food, or of permitting only broth and green vegetables for the purpose of stopping glycosuria and acidosis is unnecessary, and, unless other effects of starvation are desired besides these, one may secure all the advantages and none of the drawbacks by a diet containing up to 2.0 grams of fat per kg. of body weight; to which, except in the most difficult cases, 0.5 to 1 gram of protein per kg. and a little carbohydrate may be added. It is needless to say that an "optimal" diet is not necessary in milder cases, nor one to be recommended when the extra calories are not needed.

Disturbances of Carbohydrate Metabolism, Other than in Diabetes Mellitus . . . . . *Isidor Greenwald*

Introduction—Note on the Chemical Nature of the Carbohydrates—Pentosuria—Distribution of Pentoses—Alimentary Pentosaria—Essential Pentosuria—Fructosuria—Fructose—Fructose Tolerance—Lactosuria and Galactosuria—Pathognomonic Factors—Other Melliturias—Maltosuria—Dextrinuria—Heptosuria—Inosituria—Glycuronic Acid in the Urine—Notes on Hyperglycemia, Hypoglycemia and Other Conditions Related to Disturbed Glucose Metabolism—Glucose Metabolism.

Disturbances of Carbohydrate Metabolism, Other than in Diabetes Mellitus

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NEW YORK

Introduction

Diabetes mellitus is *the* great disorder of carbohydrate metabolism. But there are several other conditions already known and, possibly, more that are yet to be discovered in which there is a partial or complete failure to oxidize certain carbohydrates. As with diabetes, these conditions are generally recognized by the appearance, in the urine, of a substance capable of reducing alkaline copper solutions. Though these conditions may be relatively infrequent, it is important that the possibility of their occurrence be kept in mind, so that patients should not be distressed by the belief that they have diabetes when, in reality, their disorder is quite different, generally of much less importance, and often quite harmless. There have been several reported cases in which the patient has undergone long, burdensome and expensive treatment for diabetes but in which only the innocuous pentosuria existed. The number of unreported and undiscovered cases is probably much larger.

It is, of course, equally important that a mild diabetes be not mistaken for pentosuria, or similar disorder, and consequently neglected and permitted to develop into a severe type of the disease.

An abnormality in the katabolism of carbohydrate may, conceivably, involve:

1. A complete or partial failure to utilize one or more carbohydrates. In such case, these might be expected to appear in the urine.

2. A similar failure to oxidize, not the carbohydrate, but one or more intermediate products of its katabolism. This condition might manifest itself in the appearance of these substances in the urine and, possibly, in the expired air. A change in the value of the respiratory quotient might also be observed.

3. The occurrence of an abnormal path of katabolism. If the end-products of such abnormal katabolism were also carbon dioxid and water,

it might be very difficult to obtain evidence of the nature, or even existence, of the anomaly. But if this were not the case, the condition would be revealed as in the previous instance.

It will, perhaps, serve to make this a little clearer to remind the reader that the excretion of acetone, aceto-acetic acid and β-hydroxybutyric acid in diabetes and other conditions is due to disturbance of fat metabolism which belongs in one, or both, of these last two categories.

4. Other abnormalities that cannot be so readily classified. Such are found in connection with disease of the thyroid, adrenal and pituitary. Some such disorder of carbohydrate metabolism is probably concerned in the etiology of some kinds of obesity.

So little is known of the intermediate stages of the katabolism of carbohydrate that it is difficult to determine any deviation from the normal in this regard. The presence of lactic acid in the urine in acute yellow atrophy of the liver, phosphorus poisoning, etc., is unquestionably an example of either the second or third of these classes of abnormalities. The occurrence of many severe disturbances within either of these classes is made somewhat improbable by the finding of normal respiratory quotients in a large number of pathological conditions (Barr and Du Bois, Coleman and Du Bois(*b*), Du Bois(*b*), Meyer and Du Bois, Murphy Means and Aub, Peabody Meyer and Du Bois). But it should not be forgotten that slighter anomalies of metabolism would not betray themselves by changes in the respiratory quotient. They would, however, be expected to affect the carbon elimination in the urine. It is quite possible that studies of the carbon distribution, or partition, in the urine, particularly after removal of most of the nitrogenous constituents with acid mercuric nitrate or similar reagent, would have results as interesting as those that have been obtained in studies of the nitrogen partition.

The known disorders of carbohydrate metabolism are then chiefly of the first class, those that manifest themselves by the excretion, in the urine, of carbohydrate in quantities exceeding the normal. That carbohydrates are normal constituents of urine may be regarded as established, though their nature is not definitely known. Their demonstration requires special methods, and their presence is not likely to be mistaken for the occurrence of a pathological condition. (Benedict, Osterberg and Neuwirth.)

Note on the Chemical Nature of the Carbohydrates

Before discussing the individual melliturias, it may be well to consider for a moment the chemical nature of the carbohydrates. They are hydroxyaldehydes and ketones. Each carbon atom, but one, is combined with an alcohol, or OH group. The exception is either at the end of the chain and in an aldehyd, or CHO group, or is next to the end and in a

ketone, or CO group. Sugars containing the former are known as aldoses and those with the latter as ketoses. Aldoses and ketoses which differ only in this respect, having the remainder of the groups similarly arranged, are closely related and yield the same phenylosazone. The property of reducing solutions of metallic salts depends upon the presence of the aldehyde or of the ketone group. The carbohydrates that we shall have to consider in this chapter are the pentoses, hexoses and heptoses, containing five, six and seven carbon atoms, respectively, and the derivatives and combinations of these simple sugars. Although all the sugars of any one class, such as the hexoses, have the same empirical chemical formula, $C_6H_{12}O_6$ in the case of the hexoses, many of their properties are quite different. These differences are connected with differences in the arrangement of the atoms within the molecule.

All the sugars are optically active, that is, are capable of rotating the plane of polarized light. Each simple sugar has its optical antipode, or isomer, which rotates polarized light to the same degree, but in the opposite direction. The following diagrams represent the accepted molecular constitution of some of the sugars and may be useful in the discussion that is to follow.

CH_2OH	CH_2OH	CH_2OH	CH_2OH
HOCH	HCOH	HOCH	HCOH
HOCH	HCOH	HCOH	HOCH
HCOH	HOCH	HOCH	CO
CHO	CHO	CHO	CH_2OH
d-arabinose	*l*-arabinose	*l*-xylose	*d*-xyloketose

CH_2OH	CH_2OH	CH_2OH	COOH
HOCH	HOCH	HOCH	HOCH
HOCH	HCOH	HOCH	HOCH
HCOH	HCOH	HCOH	HCOH
HOCH	HOCH	CO	HOCH
CHO	CHO	CH_2OH	CHO
d-glucose	*d*-galactose	*d*-fructose	*d*-glycuronic acid

The prefixes *d* and *l* do not refer to the actual rotatory activity of the sugars. They were introduced by Emil Fischer, and are based upon the derivation of the sugar from the common dextrorotatory sugars, glucose and galactose, and their optical antipodes. Therefore, though levulose is levorotatory, it is known as *d*-fructose, because it may easily be derived from, and has the same configuration as, *d*-glucose. Similarly, the actual rotation of polarized light by the arabinoses and xyloses is the opposite of that indicated by the prefixes.

Because optical activity is a property of all sugars, the terms

"dextrose" and "levulose" have been discarded by chemists, who now use "*d*-glucose" and "*d*-fructose" instead.

All the simple sugars reduce alkaline copper solutions. For the identification of the sugar, other properties are employed. The more important of these are fermentability, optical activity, certain color reactions, ease of oxidation by bromin, the formation of phenylhydrazones and phenylosazones upon treatment with phenylhydrazin or its derivatives and the determination of the optical activity, melting point and nitrogen content of these hydrazones and osazones.

Pentosuria

Distribution of Pentoses.—Pentoses, in the form of compounds known as pentosans, are widely distributed in plants. These pentosans are the chief constituents of the vegetable gums, such as gum arabic, gum tragacanth, wood gum, etc. Just as starch yields glucose upon hydrolysis, the pentosans yield *l*-arabinose and *l*-xylose. To some extent these also occur as glucosides in various plant tissues. Another pentose of wide distribution is *d*-ribose, which is a constituent of many nucleic acids.

Alimentary Pentosaria.—Xylose and arabinose are utilized to a varying degree by different persons. The greater part, 60 to 98 per cent of doses of from 10 to 50 grams, always disappears (Bendix and Dreger). This is not due to the action of the bacteria of the intestinal tract, for similar results were obtained with subcutaneous injection (F. Voit(*a*), 1897). However, it appears that some always appears in the urine and that, too, quite promptly. Even with doses so small as 0.05 gram of xylose, a trace may be found in the urine, and with 0.25 gram there is enough to reduce Fehling's solution (Ebstein)(*e*).

Accordingly, it is not surprising that traces of pentose should occasionally be found in the urine, particularly after the ingestion of considerable quantities of fruit-juices, berries, etc. But this condition is quite different from that of essential pentosuria, in which pentose is found in the urine, no matter what the diet, and even in fasting.

Essential Pentosuria.—*Occurrence.*—The condition known as essential pentosuria was first described by Salkowski and Jastrowitz. Other cases have been reported by Blumenthal(*a*) (2 cases, Bial(*a*)(1900) (2 cases), Meyer, Brat (2 cases), Bial(*b*)(1904) (4 cases), Adler and Adler, Luzzatto, Jolles(*b*), Tinteman, Janeway(*a*) (2 cases), Adler(*b*), Klercker (2 cases), Rosenfeld (2 cases), Blum(*c*) (2 cases), Erben(*d*), Schüler (2 cases), Aron(*b*), Elliott and Raper, Levene and La Forge, Cassirer and Bamberger, Zerner and Waltuch (2 cases), Hiller and by Alexander (first case), so that there are now more than 35 well-authenticated cases. In addition, there are a number of others such as those reported by Colom-

bini, Alexander and others in which the diagnosis is not thoroughly established.

The disorder is not common. Salkowski(*d*)(1899) tried for six or seven years to discover new cases, but succeeded in finding only two in addition to the one he first described. These were reported by Blumenthal(*a*). Adler(*b*), working at Carlsbad, examined 7,726 urines, of which 1,490 reduced alkaline copper solutions. Of these, only two were pentose urines. A more frequent occurrence is indicated by the results of Jolles(*a*)(1905), who reported having found four pentose urines in 3,000, examined in the course of two years. A still greater proportion of pentose urines is claimed by Stookey. In two years he had one hundred urines that gave a slight reduction with Fehling's solution. Of these, fifteen gave pentose reactions. He believes he excluded all alimentary pentosuria. The total number of urines examined is not given but, if Stookey's results are correct, pentosuria cannot be quite so unusual as is generally believed.

Causation.—The etiology is unknown. In one case (Rosenfeld), the urine is definitely stated to have been regularly free from reducing substances up to not more than one and three-quarter years before a railway accident, in which the patient suffered trauma and shock, and after which the pentosuria was observed. The disorder has been observed at as early an age as five years (Aron(*b*)). The condition is approximately three times as frequent among men as among women.

A congenital factor is almost certainly involved in some cases. In only twenty-one cases is the family history reported, but of these nine come from four families. In addition to these, there are nine others in which diabetes is said to have existed in the family. It is quite likely that some of these "diabetes" were, in reality, pentosurias. A real connection with diabetes may exist, but a definite conclusion is unwarranted in view of the uncertainty as to the diagnosis of diabetes in many cases. The relatively frequent occurrence of pentosuria among Jews (seven patients in six families are definitely stated to have been Jews) may help to account for the frequent occurrence of diabetes in the family history. Moreover, a member of a diabetic family is more likely to wish to have his urine examined frequently than is the member of a non-diabetic family, and an existing pentosuria is therefore the more likely to be detected. The frequent occurrence of neurasthenia, or of a neurotic condition in the patient or his family may, similarly, be connected with the large number of Jewish patients, or with the effect upon the patient of the diagnosis of a persistent diabetes. Moreover, an innocuous condition such as pentosuria is more likely to come to the attention of the physician when occurring in a neurotic individual.

Diagnosis.—The condition appears to be unrecognized by the patient until the urine is examined because of some other illness or in the course

of application for life insurance. It is found to reduce the customary reagents, though more slowly. An apparent glucose content of 0.1 to 1 per cent is indicated.

Neuberg(*c*)(1902) has explained the delayed reduction as being due to the presence of a part of the pentose as a ureide, or compound with urea. He found that the reducing power of a pentose urine was increased by boiling with acid and that the reduction was then prompt, that pentose added to normal urine reduced promptly, and that the amount of pentose, as calculated from the amount of furol obtained on distillation with hydrochloric acid, was greater than that obtained by the copper reduction methods on the unhydrolyzed urine. But this explanation and, indeed, the very fact of a delayed reduction have been challenged by others.

Examination shows that the reducing substance cannot be glucose. It is not fermented by yeast, shows little or no optical activity and yields a phenylosazone of widely different melting point and nitrogen content from phenylglucosazone, but agreeing with those found for pentosazone.

The orcin test is also useful as indicating the presence of pentose. The urine is heated to boiling with an equal volume of concentrated hydrochloric acid and a little orcin. If pentose is present, the mixture will turn green (red by transmitted light) to blue or violet, depending upon the amount of pentose. If the amount of pentose is considerable, a precipitate will be produced. If the mixture is allowed to cool and is then extracted with amyl alcohol, this will take up a green to blue or violet color. Or, if the mixture is cooled to room temperature, filtered and the precipitate washed with cold water and then dissolved in alcohol, this will be colored blue and show a sharp absorption band at or near the yellow D line of the spectrum. The test should be carefully controlled by using urine and acid without orcin, a normal urine with both reagents and a normal urine with added pentose.

A similar test with phloroglucin was formerly much used but has since been found to be readily obtained with other sugars and derivatives.

Variety of Pentose Found.—The character of the pentose was first investigated by Neuberg(*b*)(1900), who isolated inactive arabinose from the urine of one of the cases reported by Salkowski and by Blumenthal. Because of the usual optical inactivity of the urine and probably also because l-arabinose is one of the naturally occurring pentoses, it has generally been assumed that the pentose is i-arabinose. But lack of optical activity is usually of little significance because the concentration of the pentose, as determined by a copper reduction method, is too low to permit of a satisfactory polariscopic examination. Of those instances in which the concentration was sufficiently high, dextrorotation has been reported in ten cases and optical inactivity in only five, including the one reported by Neuberg. This is not the place for a complete discussion of the nature of the evidence, but it may safely be concluded from the work of Elliott

and Raper, Levene and La Forge, Zerner and Waltuch and Alma Hiller that in many cases of pentosuria the carbohydrate is certainly not i-arabinose but is probably d-xyloketose. Thus, there appear to be at least two types of pentosuria.

Derivation.—It was quite natural that pentosuria should be regarded as a manifestation of defective carbohydrate metabolism, and that an attempt should be made to connect its occurrence with that of diabetes. Külz and Vogel reported the finding of small amounts of pentose in the urine of patients with severe and moderately severe diabetes, and these findings were confirmed by W. Voit (1908-9). But the amounts found were always small, never more than 0.2 gram per day and generally much less. Külz and Vogel also obtained pentosazone from the urine of depancreatized dogs and of phlorhizinized dogs. It is noteworthy that neither Külz and Vogel nor Voit controlled their technic by similar trials with normal urines, with and without the addition of glucose. It appears to the author that their results may have been due to an increased ingestion of pentoses and pentosans, to an increased nuclein metabolism, or to an increased protein metabolism. The significance of the last will be more apparent presently.

The effect of the ingestion of large amounts of glucose upon the excretion of pentose has repeatedly been studied with consistently negative results (Bial(*a*) (1900), Brat, Erben(*d*), Klercker, Schüler, Tinteman). Neuberg(*b*)(1900) has suggested the derivation of arabinose from galactose. The hypothesis does not account for the optical inactivity of the arabinose. Experiments have led to so small an increase in the excretion of pentose after the administration of relatively huge amounts of galactose as to be quite without significance (Bial and Blumenthal, Klercker, Luzzatto, Schüler, Tinteman). However, in none of these cases is it certain that the excreted pentose was arabinose. It is possible that the ingestion of galactose would increase the excretion of pentose in arabinosuria.

Experiments with l-arabinose and l-xylose (Bial, Erben(*d*) Tinteman) showed that these pentoses are as well utilized in pentosuria as they are by the normal subject. But the pentose normally excreted by these subjects was probably neither l-arabinose nor l-xylose. There seem to have been no experiments in which the patient received the same pentose as he was excreting. Such are much to be desired.

It has also been suggested that the pentose of the urine is derived from that of some of the nucleic acids of the tissues. But feeding large amounts of calf thymus is without effect upon the excretion of pentose (Bial and Blumenthal, Blum(*c*), Janeway(*a*), Tinteman), nor is there any other evidence of an increased nuclein metabolism such as would be furnished by an increased excretion of uric acid or of phosphoric acid. The amount of pentose excreted would certainly call for a tremendously exaggerated

nuclein metabolism, involving, in some cases, a complete change of the pentose in the body in less than twenty-four hours.

It is most noteworthy that, of the more than thirty-five well-defined cases of pentosuria, none approaches diabetes in severity. It is probable that such severe cases do not exist, for, if they did, they should be the first to be observed. The failure of carbohydrate metabolism, if it be such, is never complete, nor even severe. At worst, it is only a slight impairment.

It is remarkable that more attention has not been paid to the possibility of the formation of pentose from non-carbohydrate material. Klercker observed that the diurnal curve of pentose excretion ran remarkably parallel with that of urea excretion, but he connected this only with a possible derivation of pentose from the carbohydrate radical of protein, glucosamin. He fed glucosamin to both his patients without affecting the pentose excretion. He did not try other protein constituents.

It appears to the author that the known facts regarding pentosuria are best explained by the hypothesis that the condition is due to an anomaly in the metabolism of one or more of the amino-acids. Those first to be considered are those containing five or more carbon atoms in a straight chain, such as leucin, normal α-aminocaproic acid, glutamic acid, lysin or ornithin. This hypothesis is not contradicted by any known fact. It is in harmony with the apparent differences in the character of the pentoses excreted, with the optical inactivity of some and the activity of others, and with the consistently small amounts excreted. The different pentoses in the urine may be derived from different amino-acids. Direct experimental evidence is lacking, but the hypothesis is presented in the hope that those who may have the opportunity of studying cases of pentosuria will put it to the test.[1]

Fructosuria

Fructose.—*Recognition.*—Soon after the introduction of polariscopic examination of urine it was discovered that the observed rotation was frequently less than that calculated from the content of reducing, or fermenting, substance, assuming that to be glucose. The difference was not due to the presence of protein and indicated the existence of a substance of unknown nature. Instead of recognizing clearly that nothing but the difference between observed and calculated rotation was known, some of the earlier observers assumed it to be due to the presence of fructose.

[1] Since the above was written, Cammidge and Howard have reported seven additional cases of pentosuria. Only one of these patients was a woman. Three were Jews, two of whom were uncle and nephew. Two others were Greeks, father and son. The melting points of the various derivatives indicate that the pentose was inactive arabinose in all cases. The free sugar was isolated from the urine of three of the patients. In the one patient studied, the excretion of pentose in the urine fell from 3.2 gm. per day to 0.5 gm. as the protein intake was reduced and then gradually rose again as the protein intake was increased.

But with the discovery of β-hydroxybutyric acid and of the conjugated glycuronic acids it became clear that more direct evidence was required.

In some cases, it is true, the difference between the results obtained by reduction or fermentation methods and by observing the optical rotation were too great to be accounted for by any likely amount of β-hydroxybutyric acid or of conjugate glycuronic acids. But the preparation of the urine for polariscopic examination may have removed some of the glucose. In most cases, the urine must be clarified. Basic lead acetate was formerly extensively used for this purpose and no particular attention seems to have been paid as to the amount so used. It has since been shown that basic lead acetate will, under certain conditions, precipitate sugars. These conditions are generally realized in urine. The normal acetate is less effective in this regard and, in small quantities, may be used in *acid* urine without danger of loss of sugar.

Still another source of error is the faulty character of the reduction methods employed. Most of these are by no means so accurate as was formerly supposed to be the case. Funk(*a*) showed that the difference between the values obtained by Bang's method and by the use of the polariscope disappeared when Bertrand's method was substituted for the former. These results were confirmed by Borchardt(*a*)(*b*).

It is essential that other methods be employed to establish the presence of fructose. The levorotation, or the difference between reduction and polariscopic methods, must disappear after fermentation. Seliwanoff's reaction and the formation of the methylphenylosazone, both under carefully controlled conditions, should be employed as confirmatory tests.

The former of these depends upon the production of a red color upon heating with hydrochloric acid and resorcin. The test is probably best carried out as follows: The urine is mixed with one-half its volume of concentrated hydrochloric acid, heated to boiling for half a minute and divided into two portions, one of which serves as a control. To the other are added a few crystals of resorcin and it is again heated to boiling for a few seconds. The presence of fructose is indicated by the appearance of a red color. The mixture should be cooled, made alkaline with solid sodium carbonate and extracted with ethyl acetate, which will take on a yellow color. Prolonged boiling or the addition of a greater quantity of acid should be avoided or glucose will also react. For this reason the test should be controlled by another, using normal urine containing added glucose in amount equivalent to the reducing action of the urine under examination.

Methylphenylhydrazin was recommended by Neuberg(*c*)(*d*)(1902, 1904) as reacting specifically with ketoses, such as fructose, and not with aldoses, such as glucose, to form the osazone. However, Ofner showed that, under certain conditions, glucose will also react with methylphenylhydrazin. The osazones formed from the two sugars are, of course,

identical. Therefore, it is important that the test be controlled by a similar test with normal urine containing added glucose.

Occurrence.—If the voluminous literature on the subject of the occurrence of fructose in diabetic urines be reviewed, it will be found that few reports will stand critical examination. In most of those in which the evidence at first seems strongest the urine contained five per cent, or more, of glucose. In none of these can the tests applied be considered to have been properly controlled, so that the actual presence of fructose may well be doubted. Moreover, in the light of what we now know of the ready conversion of glucose into fructose in the presence of weak alkalies (Lobry de Bruyn and van Ekenstein), the small amount of fructose reported may have, in some cases at least, been formed after the secretion of the urine.

There remain, however, a number of cases in which the presence of fructose may be regarded as established. With few exceptions, these are cases of pure fructosuria, only the one sugar appearing in the urine. These include those reported by Seegen (also by Külz), Rosin and Laband, Schlesinger, Lepine and Boulud(*b*), Neubauer(*a*), von Moraczewski(*b*), Borchardt(*b*), Adler(*b*), and by Strouse and Friedman. In addition, there are a number of cases such as that reported by Czapek(*b*) and by Zimmer(*a*), and others by May, Lion and others, in which the presence of fructose is indicated but in which the identity of the levorotatory substance was not satisfactorily established.

One of the most interesting of these doubtful cases is that of Czapek and of Zimmer. The patient was a military surgeon, twenty-nine years old, who had had an attack of icterus eleven years previously. When first observed, he was excreting 2,500 to 3,000 c.c. of urine a day, with a sugar content, determined by titration, of 2.5 to 3 per cent. Later, even on a strict diet, this rose to 10 per cent, with a total excretion of four or five liters a day. After a course of treatment at Carlsbad, the volume of urine dropped to 1,500 c.c. and the sugar content to one per cent. In spite of the high reducing power, both Czapek and Zimmer found the urine to be levorotatory. There can be little question here of errors inherent in the analytical procedure, for Czapek expressly states that an *acid* urine containing 6.6 per cent of glucose by titration with Fehling's solution was cleared by the addition of a little powdered *neutral* lead acetate and then showed a *rotation* of 1 per cent. If the presence of β-hydroxybutyric acid be held responsible, the required concentration would be 16 per cent and, in some other specimens, even more. It would seem that this was really a case of diabetes complicated by fructosuria.

Apart from its possible occurrence in diabetes, fructosuria is a rather rare condition. In the series of examinations at Carlsbad, already alluded to in the discussion of pentosuria, Adler found only two cases of fructosuria in 7,726 urines, 1,490 of which reduced Fehling's solution.

The concentration of fructose in the urine may be as high as 3.5 per cent but is generally less than 1.5 per cent.

Since it is found in the urine, it is to be expected that fructose would also be present in the blood. Rosin and Laband have, indeed, reported that they observed this, but their figures are so remarkable, over 0.5 per cent by polarization in the blood when there was only 1.4 per cent by reduction in the urine, as to make one suspect their analytical procedure. Neuberg and Strauss reported the isolation of methylphenylfructosazone from the serum, ascitic and pleural fluids of several different patients, particularly after the administration of fructose. These patients did not exhibit a spontaneous fructosuria. A close examination of their figure yields some interesting results. In their Expt. 4, 1,470 c.c. of pleural fluid from a patient with lymphoma, but no fructosuria and not receiving fructose, except in the quantities present in an ordinary diet, yielded 1.35 grams of the osazone. Since 2 grams of fructose added to 200 c.c. ascitic fluid yielded 2.27 grams of osazone, the 1.35 grams of osazone represent at least 1.19 grams of fructose or a content of 0.081 per cent in the pleural fluid taken. The other experiments give similar results. In other words, if the work of Neuberg and Strauss was valid, practically all of the sugar of these fluids was fructose and little, if any, was present as glucose. This is extremely improbable. It is much more likely that the osazone was formed from glucose, particularly since Ofner obtained the osazone from pure glucose under very similar conditions. The presence of fructose in the body fluids is yet to be demonstrated.

The ingestion of starch, lactose or glucose (Schlesinger, Neubauer(*a*), Borchardt(*b*), 1909b) is without effect on the excretion of fructose. This is increased by the administration of fructose or its compound, sucrose (cane-sugar). The increase is not so great as the amount ingested. The exact fraction eliminated appears to vary considerably. Neubauer found that 16 per cent of any amount from 3.8 to 50 grams appeared in the urine. But others (Schlesinger, Borchardt(*b*), Strouse and Friedman) have found from 2 to 20 per cent of the amount ingested in the urine and more with larger amounts than with smaller. Only Rosin and Laband failed to find that the ingestion of fructose increased its excretion in the urine. But their experimental work seems to have been decidedly faulty and no great significance should be attached to their report.

Treatment.—The therapy is obvious: withdrawal of sucrose and honey from the diet, and a limitation of the consumption of berries, fruits, etc. The sugar then disappears from the urine or occurs in minimal amounts.

Significance.—Fructosuria is not an apparently harmless anomaly like pentosuria. It is a real disorder and is to be compared to a mild diabetes. However, there is no record of its developing into diabetes. The prognosis is good.

The claim of Cammidge that so-called urinary fructose is frequently

"isoglycuronic acid" cannot be allowed. In one paper (1915) the melting points of four different preparations of the p-bromphenylosazone of the substance from urine are given as 196°, 197°, 197° and 198°. In another paper (1916) it is given as 236°, and that of "true levulose" as 197° and of dextrose as 220°. But the fact is that the p-bromphenylosazone of glucose is identical with that of fructose and melts at 222°. On having his attention called to this, Cammidge (*d*) replied that this was due to an error. Substituting the values given in his letter this sentence would read, "The (p-bromphenyl) osazone of pseudolevulose melts at 197°, that of true levulose at 220°, and the osazone of dextrose at 220°, while the hydrazone of glycuronic acid melts at 236°," which certainly does not indicate that Cammidge realized that the compounds obtained from "levulose" and "dextrose" were identical. The melting point of the unsubstituted phenylosazone of the "pseudolevulose" is given as 223°, "7° lower than the melting point of dextrosazone and levulosazone." But the melting point of this compound is generally accepted at 204°-205°. In his letter, Cammidge ascribes the difference to his use of the Maquenne block instead of a capillary tube for the determination. For the value of 230° for the melting point of phenylglucosazone, Cammidge has the high authority of Bertrand. But Müther and Tollens found that the melting point of glucosazone to be practically the same by either method, with somewhat greater variability when using the block. Certainly, it is strange that Cammidge and Howard should observe a difference of 25° with one compound and none, or very little, with two others (the p-bromphenylhydrazin compound of glycuronic acid and the p-bromphenylosazone of fructose or glucose). Cammidge and Howard identify their "isoglycuronic acid" by oxidation to arabonic acid with lead peroxid and sulphuric acid, a reaction not described elsewhere in the literature as employed for any closely related purpose, and then prepare the barium salt by boiling with barium carbonate. This salt is then decomposed by passing carbon dioxid into an aqueous suspension and boiling. Why the reaction should so easily reverse itself is not explained. No substance having the properties ascribed to "isoglycuronic acid" by Cammidge has been described by others. It would seem that work involving such new chemical reactions and observations should not be casually published in a medical journal, as if well-known and established, but should be fully described in a chemical publication where it would come directly to the attention of chemists.

Fructose Tolerance.—*Test for Hepatic Function.*—In 1901 Strauss (*b*) described a fructose-tolerance test for hepatic function. He found that patients with evidence of hepatic disorders, other than passive congestion, excreted at least a small part (1 or 2 gm.) of 100 gms. of fructose taken on a fasting stomach. Of patients with other conditions, only 6 out of 58 gave positive reactions. With the exception of Landsberg, most other workers have confirmed the diminished tolerancy in marked hepatic dis-

orders, though the diagnostic value of the test has not been generally accepted (Rowntree, Hurwitz and Bloomfield). The reaction is frequently positive in other conditions such as acute infectious diseases (typhoid, pneumonia, etc.), in pregnancy and, of course, in disorders of the endocrin glands. (Franke, Friedman and Strouse, Keller.) In many of these cases there is no other sign of hepatic insufficiency. Nevertheless, it is claimed that the alimentary fructosuria itself demonstrates the existence of such, which is regarded as being either too slight to be manifested in any other manner or else to affect only this particular function of the liver. But this is merely begging the question. It would appear to be more accurate to say simply that the capacity of the organism to utilize ingested fructose has been diminished, leaving the location of the metabolic fault to further investigation. It may be that the liver itself is perfectly normal, but is unable to function properly in this regard because some hormone derived from the thyroid, pituitary or other gland is present in excessive, or deficient, amount, just as a machine will not work effectively if supplied with too much, or too little, or the wrong kind of, lubricant.

Lactosuria and Galactosuria

Pathognomonic Factors.—*Occurrence.*—For many years it has been known that in the late stages of pregnancy, while nursing and, more especially, upon the weaning of their children, women excrete varying amounts of lactose in the urine. The concentration is only rarely more than 0.5 per cent. The origin of the sugar is obvious. Zülzer(*a*) observed that women had a lower tolerance for ingested lactose during the period from two to eight days after delivery than normal or pregnant women had. They also reacted to a glucose tolerance test by the excretion of lactose. He offered the teleological explanation that the diminished tolerance of the organism of the mother for lactose was designed for the protection of the offspring. It is more probable that the lowered lactose tolerance is due to the fact that the organism is already, so to speak, saturated with lactose and that the effect of glucose is due merely to an increased formation of lactose, according to the laws of mass action.

Of quite different significance is the appearance of lactose in the urine of sucklings. Although the excretion of a sugar had been reported as early as 1869, its nature was not known until 1892, when Grosz showed that it was either lactose or galactose, that it was of alimentary origin, and was found only in cases of gastro-intestinal disease. Langstein and Steinitz completed the demonstration that it was almost always lactose, though there might also be some galactose. They also found it only in children with gastro-intestinal disorders. They showed that the condition was not due to the absence of lactose from the intestine, for they were

always able to demonstrate the presence of the enzyme in the feces. Apparently, we are here concerned with an abnormal permeability of the gastro-intestinal mucosa, which permits the absorption of lactose, before it has been split into glucose and galactose. The liver and other organs can effectively handle these sugars only, not their combination, lactose.

The same explanation will probably apply to the results of von Halasz, who observed that in twenty-two out of twenty-three cases of carcinoma or dilatation of the stomach, the ingestion of 150 grams of lactose was followed by the appearance of lactose in the urine, whereas in forty-five other individuals with a variety of pathological conditions, including eight with cirrhosis of the liver, two with echinococcus cysts of the liver and four with carcinoma of the esophagus, liver or gall-bladder, this result was not obtained.

Bauer found that the ability of the organism to utilize 30 or 40 grams of ingested galactose was seriously depressed in certain hepatic disorders. The excretion of traces of the sugar in the urine had no particular significance, slightly larger amounts were found in various hepatic conditions in which the parenchyma might be considered to be affected, and more than four grams in the urine was indicative of catarrhal icterus, acute yellow atrophy, phosphorus poisoning, etc. Other workers (Rountree, Hurwitz and Bloomfield, Wörner and Reiss) have, in general, confirmed Bauer's results, although there have also been reports of the occurrence of alimentary galactosuria in nephritis and in Basedow's disease (Maliwa). As in the case of alimentary fructosuria, this may be due to a coexisting hepatic dysfunction, though other evidence thereof is lacking.

Recognition. Lactose and galactose are both dextrorotatory, $[\alpha]_d^{20}$ + 55.16° and + 81°, respectively, and both reduce alkaline copper and alkaline picrate solutions. Galactose is fermented by yeast, though more slowly than glucose. Lactose itself is not fermented but, as the test is ordinarily performed, it may be split into glucose and galactose by some contaminating organism and the simple sugars then fermented by the yeast. Positive proof of the presence of galactose, free or combined, is best obtained with the mucic acid test. To the urine or the filtrate from precipitation with mercuric nitrate, add one-tenth volume of concentrated nitric acid (sp. gr. 1.42) and evaporate on the water bath to a little more than the volume of the nitric acid added. After standing twenty-four hours, add one-half volume of water and allow to stand another twenty-four hours.

Mucic acid crystallizes out in minute, rhombic prisms, which melt at 212°-215°. The crystals obtained may be purified by filtering, washing with a little water, dissolving in dilute ammonium hydroxid, filtering, evaporating to dryness and adding 5 c.c. dilute nitric acid (sp.gr. 1.15). The crystals may now be filtered, washed with a little water, alcohol and

ether, dried and weighed. One part mucic acid represents 1.33 parts galactose. Whether originally free or combined must be determined from a comparison of the reduction, polarization and mucic acid yield.

Other Melliturias

Maltosuria.—Maltose has frequently been supposed to be present in diabetic and other urines. But the evidence therefor is quite unsatisfactory. Geelmuyden(*b*) attempted to separate maltosazone by fractional crystallization of the osazones from diabetic urine. He obtained from the more soluble fraction crystals melting between 192° and 207°. Since glucosazone melts at 205° and maltosazone at 202°-208°, it is evident that the melting point will not serve to distinguish them. Geelmuyden claimed that crystals having this high solubility were not obtained from glucose, and that they could be isolated from mixtures of maltose and glucose only when the former constituted 10 per cent, or more, of the mixture. But it is quite possible that some urinary constituent increased the solubility of some of the glucosazone. It is unfortunate that Geelmuyden did not control his procedure by means of experiments with glucose added to normal urine and that he did not identify the maltosazone in some other way. Maltosuria was also reported by von Ackeren in a case of carcinoma of the pancreas, and by Rosenheim in a case of chronic pancreatitis, but their evidence is similarly insufficient. Rosenheim did, indeed, determine the nitrogen content of the osazone, but he did not present details and figures so that it is impossible to judge of the accuracy of his interpretation of his results. The importance of having all the data will be more evident presently.

Lepine and Boulud(*a*) reported the presence of maltose in the urine of a diabetic, and in that of a depancreatized dog. The claim is based entirely upon the difference between the values obtained by polarization and by reduction methods, and the disappearance of this discrepancy upon hydrolysis with hydrochloric acid. But examination of their figures shows that these were not identical after hydrolysis. Moreover, in a control experiment with 10 grams of maltose and 40 grams of glucose, the values they obtained before hydrolysis were 63 grams by rotation, which is approximately the calculated quantity, and 31.64 grams by reduction. The calculated equivalent is about 46 grams of glucose. After hydrolysis, the values they obtained were 40.5 grams by rotation and 35.2 grams by titration. The calculated value is 50.28 grams for both. What became of about 15 grams of sugar is not indicated. Kottmann's report is similarly discredited.

A report that carries more weight is that mentioned by Neuberg(*d*) (1911) of a case observed by Magnus-Levy. The urine showed a marked

excess of dextrorotation over that calculated from the reducing power. After hydrolysis with hydrochloric acid, this difference disappeared. After fermentation, both rotation and reduction disappeared. The calculated content was 1.5 per cent maltose and 2 per cent glucose.

The last report represents nearly all that is necessary to a diagnosis of maltosuria. In addition to the determinations made, the osazone should be prepared, recrystallized and melting point, nitrogen content and optical rotation determined. 0.2 gram of osazone is dissolved in 4 c.c. pyridin and 6 c.c. absolute alcohol and observed in a 1 dm. tube. Glucosazone has a rotation of -1° 30′ and maltosazone of $+1^\circ$ 30′. This has not yet been determined for any case of supposed maltosuria.

According to von Noorden (*k*)(1907), a reducing substance is frequently present in the urine after the ingestion of beer. In some individuals, the drinking of half a liter of beer is followed by the appearance of this reducing substance in the urine. Von Noorden believes the substance to be maltose and ascribes its appearance to a deficiency in maltase in the intestine or in the blood.

Dextrinuria.—A very remarkable urine was recently reported by Gaillard and Fabré. This was obtained from a physician who had been injured by the explosion of a high-explosive shell and who had later developed nervous symptoms indicating, among other things, an involvement of the labyrinth. The urine contained a reducing substance, but the dextrorotation was far greater than was to be expected if the reducing substance were glucose. From a sample having an apparent glucose content of 36.7 grams by reduction and of 80.2 grams by rotation, Gaillard and Fabré obtained, by precipitation with alcohol, 3 grams of a dextrin having a specific rotation of $+ 206^\circ$ and giving a slight color with iodin. The filtrate still showed a difference between the values for glucose calculated from reduction and rotation, but this disappeared after boiling with dilute hydrochloric acid. From their results, Gaillard and Fabré calculated that the urine contained 3 grams dextrin, 16.6 grams maltose and 20 grams glucose.

Kotake(*a*) had observed the excretion of dextrin in the urine of a dog that had been poisoned with oxyphenlyglyoxylic acid, but had been unable to repeat the observation. Other than this dog and the case of Gaillard and Fabré, there are no well-defined cases of dextrinuria in the literature. A substance resembling dextrin has been obtained from normal and pathological urines but in much smaller amounts and requiring other methods for its isolation.

Heptosuria.—The occurrence of heptose in a diabetic urine was reported by Rosenberger. The substance reduced alkaline copper solutions but was non-fermentable and optically inactive. It formed an osazone, the nitrogen content of which indicated it to be a heptosazone, derived from a sugar with seven carbon atoms. This osazone could be converted

into the ozone and this again into the sugar. If this report is correct, it not only proves the existence of an entirely new kind of metabolic anomaly, but it may also require modification of some of our ideas regarding the intermediary metabolism of fatty acids. It is difficult to imagine any other source but these for the origin of an optically inactive heptose.

Inosituria.—Inosite, though not chemically a sugar, is composed of the same number of carbon, hydrogen and oxygen atoms as is glucose. That it stands in some physiological relation to glucose is indicated by the fact that, in the phlorhizinized dog, its subcutaneous administration is followed by an increased excretion of glucose, which becomes greater as the administration of inosite is continued. Most of it, however, is excreted unchanged both by the normal and the phlorhizinized dog (Greenwald and Weiss). Similar evidence of its poor utilization was obtained by Anderson. The reported excretion of 18 to 20 grams of inosite in the urine of a diabetic, in which it gradually replaced the glucose, is, therefore, all the more remarkable (Vohl).

Small quantities of inosite have been found in the tissues, particularly in the muscles, but the significance thereof is not evident. Its occurrence in the urine has most frequently been reported in connection with polyuria, as in diabetes mellitus, insipidus, albuminuria (Cloetta, Gallois). But Magnus-Levy(*j*) was unable to isolate it from the urine of any of his patients with diabetes insipidus and Külz(*a*)(1874-5) found it only occasionally. On the other hand, Starkenstein(*a*) regarded it as a constituent of normal urine. Whether these differences depend upon differences in technic, or upon differences in the diets of the patients, it is difficult to determine. At any rate, the significance of inosite in the human economy is problematical.

Glycuronic Acid in the Urine.—Glycuronic acid is derived from glucose by the oxidation of the terminal alcohol to an acid group. The aldehyd group, which might be expected to be the more readily oxidized, is unchanged. This is probably due to the fact that glucose combines through the aldehyd group with phenol, menthol, thymol or any one of a large number of substances, and that the oxidation takes place subsequently. Free glycuronic acid is not found in nature. It is always in combination as in phenolglycuronic acid, etc. The purpose of this combination is, presumably, detoxication. It is supposed to occur chiefly in the liver, and a failure of the organism to respond to the administration of camphor by the prompt excretion of the usual amount of conjugate glycuronic acid, has been used as a test of hepatic function (Gautier).

Cammidge Reaction.—Cammidge described a reaction in the urine which he considered to be valuable in the diagnosis of pancreatitis. The exact technic has been modified from time to time but, in its essentials, it depends upon the presence of a substance forming a phenylosazone in the hydrolyzed filtrate from a lead acetate precipitation of the urine. With-

out acid hydrolysis, no crystals should be formed. The usefulness of the test has been quite generally denied but it has found some supporters (Van Hoogenhuyze and Nagasaki, Lameris and Van Hoogenhuyze). Cammidge and Howard(*a*) regard the reaction as due to the presence of a dextrin-like substance, which they claim to have isolated and from which they prepared the free pentose, which they identified as xylose by the melting point and rotation of the osazone, and by the formation of xylonic acid upon oxidation of the pentose with bromin. But analysis of the substance gave 43.8 and 43.6 per cent. carbon and 6.2 and 6.3 per cent. hydrogen, which would correspond to a hexosan $(C_6H_{10}O_5)_n$, for which the calculated values are 44.4 per cent and 6.15 per cent, respectively, rather than to a pentosan $(C_5H_8O_4)_n$, for which they would be 45.5 per cent and 6.06 per cent. Cammidge proposed the alternative formula $(C_6H_{10}O_5)_n\,C_5H_9O_5$, but did not explain what value to ascribe to "n" nor how a pentosazone should have been formed from the hexose groups or what became of the hexose groups on hydrolysis. Pekelhäring and van Hoogenhuyze, who are among the few who accept the test as having any value, found quite different values for the composition of the substance. They found that the osazone contained from 11.64 to 12.71 per cent nitrogen, instead of the 16.4 to 17.1 per cent claimed by Cammidge. That the substance obtained by Pekelhäring and Van Hoogenhuyze was not a pentose is also indicated by the fact that it gave a red color, and not green or blue, upon treatment with hydrochloric acid and orcin. Other investigators have generally concluded that the Cammidge crystals are due to the presence of conjugate glycuronic acids, while Neuberg(*p*)(1912) regards them as mixture of compounds whose nature varies from case to case, though generally due to the presence of glycuronic acid.

For a discussion of the other substances of carbohydrate nature that have from time to time been reported to have been found in urine, as well as for more explicit directions for the identification, isolation and quantitative determination of the different sugars and their derivatives, the reader is referred to F. N. Schulz, in Neubauer-Huppert, "Analyse des Harns," Wiesbaden, 1910, pages 284-477; to Carl Neuberg, "Der Harn," Berlin, 1911, pages 319 to 464; and to C. A. Browne, "A Handbook of Sugar Analysis," New York, 1912.

Notes on Hyperglycemia, Hypoglycemia and Other Conditions Related to Disturbed Glucose Metabolism

In a number of conditions, apparently involving the organs of internal secretion; or endocrine glands, there is a disturbance of carbohydrate metabolism. Of these, perhaps the best known is the hyperglycemia, and occasional glycosuria, of Basedow's disease. In some cases, the hyper-

glycemia is not evident under ordinary conditions, but becomes so after the ingestion of glucose; the physiological rise in content of blood sugar being exceeded and prolonged. Exactly the contrary is the case in myxedema, in which condition the tolerance for glucose is abnormally high (Geyelin). The relation of the state of pituitary function to carbohydrate metabolism is not quite so clear, but there is no doubt that, in some cases of dyspituitarism, there is a low carbohydrate tolerance with a tendency to spontaneous glycosuria, while in others the tolerance is very high and the blood sugar is low (Cushing(*c*)). A similar low level of blood sugar is observed in muscular dystrophy (Janney, Goodheart and Isaacson, McCrudden and Sargent) and in Addison's disease (Bernstein, Porges(*b*)). In the former there is also a high tolerance for glucose. This does not seem to have been tested in Addison's disease.

The significance of these facts for diagnosis, and for our understanding of the function of the endocrine glands, will be more fully discussed in other chapters. It is here intended to offer a few observations on the possible paths of glucose metabolism, and to indicate the probable nature of the disturbances.

It would seem that there are involved three important chemical reactions, or groups of consecutive reactions, one of which is reversible while the other two are not. The reversible reaction is that of glucose $\rightleftarrows$ glycogen. The apparently irreversible actions are concerned in the formation of fat from glucose and in the oxidation of glucose. The various disturbances of glucose metabolism are then due to conditions which raise, or lower, the concentrations of blood sugar at which it is possible for these reactions to occur.

To use a mechanical analogy, the blood sugar may be compared to a mill pond, with four sluices, one to another pond, or reservoir, one to a spillway, and the other two to mills, one of which (A) uses water power directly, the other of which (B) first converts it into electric power, which may be used at once or be accumulated in storage batteries. This mill is, perhaps, located, not on the same pond as the other mill and the spillway, but on the reservoir. According as the sluice gates are raised or lowered, the water will flow in different directions. Let us assume there is water in both ponds, with none going through B, which is delivering energy from its storage batteries, while mill A is not receiving water to its full capacity. As more water is supplied, mill A uses more, and more flows into the reservoir. It may be that more water will flow through A than is required and some of the energy may be wasted. The storage batteries in B are no longer required and cease to supply energy. As the level of water rises, the reservoir fills, and mill B begins to operate and to charge the batteries. As the water reaches a still higher level it goes over the spillway.

The reservoir is the tissue glycogen, the spillway is represented by the kidneys, the two mills are, respectively, the direct oxidation of glucose

and through the formation of fat. The height of the sluice gates represents the concentration of blood sugar at which the various reactions, or series of reactions, occur. If, in addition, we assume that the electric power plant can deliver all of its energy only if some power is supplied from the first mill to operate accessory machinery, we have a picture of the possibilities of disturbed glucose metabolism.

In hyperthyroidism and similar conditions, little glycogen can be formed because the sluice between the two ponds is set too high (Cramer and Krause, Kuriyama); that is, too great a concentration of glucose is required to bring about the reaction glucose → glycogen. The sugar supplied must be oxidized or go over the spillway. In hypothyroidism, muscular dystrophy, most cases of dyspituitarism, etc. (Benedict and Homans, Cushing(*c*), Geyelin, Janney, Goodheart and Isaacson, McCrudden and Sargent(*a*)), the reservoir sluice is abnormally low, and not sufficient glucose is supplied to mill A to operate it at capacity. Added sugar does not go here to the same extent as normally, but is diverted to the reservoir and to the electric power, or fat mill. Here it may be used to furnish needed energy, which is used or else accumulated in the batteries, perhaps to an excessive degree.

In diabetes, the first mill sluice is set too high, or is choked, and more sugar goes through the fat mill. If the sluice is raised sufficiently high, some sugar goes over the spillway. This, in turn, may be raised and furnish a greater head, or pressure, for the sugar mill. If the obstruction in A is too great, not enough goes through it to operate the accessory machinery in B and "acetone bodies" appear in the urine.

Obesity might be of two kinds, one related to diabetes, due to deficient sugar oxidation and probably accompanied by high blood sugar, the other due to an abnormally low sluice to the fat mill, and accompanied by a low blood sugar. This type would occur in hypothyroidism, dyspituitarism and similar conditions. Similarly, unusual leanness might be due either to a very high sluice to the fat mill or to a very low sluice to the sugar mill. In the first case, the content of blood sugar would be high, as in hyperthyroidism, in the second it would be low, as in Addison's disease.

The high blood sugar of nephritis might be due to raising of the sluice to the sugar mill, or to the reservoir.

It should follow from this hypothesis that, in obese persons, the increase in metabolism following the ingestion of glucose should be less than in those of normal weight. This has not yet been determined. Negative results have been obtained with experiments made with mixed diets and even, in Staehelin's(*b*) case, with a carbohydrate meal. But most of this carbohydrate was starch. Glucose should be used in order to make the difference more apparent, and the total metabolism during the period of absorption should be determined. It should be remembered that only a

very small difference, continued over a long time will, especially if combined with overfeeding, produce a marked effect.

A correspondingly greater increase in metabolism following the ingestion of glucose should be observed in hyperthyroidism and in those persons who, in spite of adequate diet, remain unusually thin, without apparent cause.

This analogy has been presented and developed in the hope that it may help to a better idea of how all disturbances in the metabolism of glucose may be interrelated, and that it may lead to the formulation of new problems, the solution of which will add to our knowledge of this very interesting and important subject.

Metabolism in Nephritis . . . . . *Herman O. Mosenthal*

Introduction—Total Metabolism in Nephritis—Protein Metabolism in Nephritis—The Nonprotein Nitrogen of the Blood and Tissues in Nephritis—The Urea of the Blood in Nephritis—The Relation of the Urea to the Total Nonprotein Nitrogen of the Blood in Nephritis—Creatinin in Nephritis—Creatin in Nephritis—The Comparative Value of Uric Acid, Urea and Creatinin in the Blood in Nephritis—Amino-Acids in Nephritis—The Nitrogen Balance in Nephritis—Protein Destruction in Nephritis—Fat Metabolism in Nephritis—Phosphates and Calcium of the Blood in Nephritis—Renal Function—Tests for Function of the Glomeruli and Tubules—Schlayer's Theories of Renal Function in Nephritis—The Coefficient of Urea Excretion—Facts Regarding Renal Function that Have Been Developed by a Study of the Laws of Urea Excretion—The Chlorid Threshold in Nephritis—Tests for Urea and Salt Excretion—Test Day for Renal Function—Directions for "Test Day for Renal Function"—Uremia—Uremia, as described by Julius Cohnheim in 1882—More Recent Aspects of Uremia—Nephritis Toxicosis—Summary—Increased Arterial Pressure in Nephritis—The Influence of Food Products on Blood Pressure—Lesions in the Glomeruli—Summary.

Metabolism in Nephritis

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NEW YORK

Introduction

There has been a marked tendency in the past to regard all cases of nephritis as being a problem of renal insufficiency only. This side of the question has been worn threadbare by medical and chemical research; very far-reaching results have been achieved, but the solution of the question of what pathological processes or toxic factors are responsible for most of the signs and symptoms of nephritis, such as uremia, edema, headache, hypertension, etc., still remains unsolved. However, the problem has been more closely defined and much has been gained thereby. Three very different factors may be regarded as shaping the disease we are pleased to call nephritis. These are:

1. *Degenerative changes,* affecting principally the tubules of the kidney, which have been termed the nephroses.

2. *Inflammatory changes,* involving a part or all of the renal structure.

3. *Renal insufficiency,* which develops in its pure form in the uncomplicated arteriosclerotic kidney.

In considering these three factors it becomes very evident to the student of nephritis that the kidney is only a cog in the wheel of the clinical picture of this malady. Degeneration, inflammation, arteriosclerosis and renal insufficiency affect the blood vessels and tissues of the whole body either at the onset of the disease or secondarily. The result is an interlacing of various signs, symptoms and pathological processes that is only beginning to be unraveled. The outstanding feature of the whole situation is that renal insufficiency and its sequelæ form a clinical symptom complex, of which the effects and signs may be judged with some degree of precision, while the rôle played by degenerative and inflammatory changes remains an enigma. This is due in large part to the fact that the former is a condition whose cause is localized in the kidney, while degeneration and inflammation can not be regarded as purely renal affections, but must be looked upon as constitutional states in which every tissue in the body is involved. It is only on this supposition that many of the symptoms of

nephritis can be explained. It is proposed in the present article on the metabolism of nephritis to summarize the points concerning which some knowledge has been obtained.

Theodore Janeway once remarked that the three most important problems of Bright's disease were uremia, edema and blood pressure; to these the author would add a fourth: renal insufficiency. It may seem at first glance that the subject of uremia includes renal insufficiency; the two overlap but nothing more than that; from the clinical point of view certainly they are not identical. It is hoped that in the following pages an adequate presentation of these subjects is given, with the exception of edema, which is considered in a special section. Some phases of Bright's disease that have often been considered as having a bearing upon the subject of metabolism in nephritis have been omitted, in part because the author does not believe that the relationship is sufficiently close and in part because the knowledge concerning some of these matters is not far enough advanced to warrant an exposition.

Total Metabolism in Nephritis

The total metabolism of uncomplicated nephritis appears to be normal. There are certain complications that alter it, while others do not.

Dyspnea.—Peabody, Meyer and DuBois studied the total metabolism of patients with cardiac and renal disease and found it to be normal except when influenced by dyspnea. When this was present, the metabolism increased as much as 49 per cent above normal. The rise in the metabolic rate could not be accounted for on the basis of effort associated with the labored breathing, as the increased muscular work entailed was not sufficient; furthermore, there appeared to be no constant relation between the augmented metabolic rate and *acidosis* (as measured by the carbon dioxid tension of the alveolar air), *renal function* (as determined by the excretion of phenolsulphonephthalein) or *arterial hypertension.* What the factor or factors are that determine the high metabolic rate associated with the dyspnea is not known. Aub and DuBois substantiated the above findings, regarding an increased metabolic rate associated with dyspnea, though their two cases showed but a slight rise, as did some of the patients of Peabody, Meyer and DuBois.

Edema.—Edema is associated with a distinct reduction in metabolism. It may be very marked being as much as —27 and —40 per cent in two cases. It is only to be expected that an organism diluted by inert fluid should show a diminished metabolism according to body weight. In cases of obesity this occurs, but Means(*b*) has shown that they have the same metabolism per square meter of surface as normal people. Edematous cardiac patients as a rule show an increased metabolism, but here other

factors may be involved. The marked reduction of metabolism, as measured per square meter of surface, found in cases of nephritic edema points to some other cause than mere dilution of tissue and distention of skin (Aub and DuBois).

High Blood Pressure.—According to Aub and DuBois, this has no constant influence on the total metabolism. An increased arterial tension may be associated with cardiac insufficiency and marked arteriosclerosis. The latter may bring about a deranged function in almost any organ. It is therefore only to be expected that cases of hypertension should show wide variations in their total metabolism which are not necessarily the result of uncomplicated hypertension. An increased blood pressure without secondary changes, as the authors quoted above have shown, evidently does not affect the total metabolism.

Acidosis has little effect on the total metabolism in nephritis (Peabody, Meyer and DuBois). It is well to bear in mind that the acidosis encountered in nephritis is usually due to inability of the kidney to excrete certain acid substances which, under normal circumstances, it eliminates very readily. In the type of acidosis brought about by a diminished carbohydrate utilization, either on carbohydrate free diets or in diabetes mellitus, there may be an increased total metabolism which Lusk has ascribed to an accelerated protein consumption during the carbohydrate free periods. In cases of nephritis, associated with nausea and vomiting, or on a starch free diet, or on starvation treatment, the second form of acidosis would increase the metabolic rate in nephritis.

Renal Function.—The effect of diminished water excretion and its accumulation in the body tissues has been discussed under edema. Renal function as measured by the phthalein output, the non-protein nitrogenous constituents of the blood or Ambard's coefficient, even when it was very much impaired, did not alter the level of the total metabolism (Aub and DuBois).

Summary.—In nephritis, according to the most recent investigations, the total metabolic rate appears to be normal, except when the disease is complicated by dyspnea, which results in an increased metabolism, and when associated with edema, which lowers the metabolic level. The reason for either of these phenomena is not entirely clear.

Clinical Application.—Most cases of nephritis maintain their nutrition perfectly while on a normal diet; many of them become obese from overeating. In such individuals a normal metabolism probably exists. Uremic states, characterized by loss of appetite, nausea and vomiting, and the increased metabolism which must of necessity accompany muscular twitchings and convulsions, may play havoc with many of the scientifically calculated diets and necessitate an altered schedule of feeding if the metabolic requirements of the individual are to be met.

The loss of large amounts of albumin in the urine will in some in-

stances necessitate a readjustment of diets if nutrition is to be maintained. The albuminuria in itself may not cause an increased metabolic rate but, if marked, may result in a considerable drain upon the system which calls for replacement if it can be accomplished with safety to the patient.

There are many instances of loss of weight, and slowly or rapidly developing anemia in certain patients. These usually have marked evidences of arteriosclerosis following upon hypertension. Many of these cases, suffering with arteriosclerotic lesions in the kidneys, as well as their other tissues, have been diagnosed as uremia instead of cerebral arteriosclerosis, which they really are. The loss of weight in these persons may be ascribed in part to lack of assimilative power, which must of necessity attend a general arteriosclerosis, and in part to a diminished appetite. Exactly what rate the basal metabolism assumes in these individuals is an open question.

In some patients an accelerated destruction of protein occurs. This may assume considerable proportions. This question will be taken up in greater detail under the heading of protein metabolism.

Protein Metabolism in Nephritis

Protein metabolism in nephritis has always been regarded as the pivotal point about which the signs and symptoms of nephritis grouped themselves. This conception was the natural outcome of the fact that the kidney excreted the end products of protein katabolism while those of the fats and starches were largely eliminated through other channels. There are certain very definite changes that occur in the body due to the retention of the waste substances derived from the proteins. However, the realization that renal insufficiency is not alone responsible for the phenomena occurring in nephritis has been slowly forced upon the clinician by the extensive use of the recently perfected methods in blood chemistry; many cases of nephritis, exhibiting marked symptoms, apparently have no disturbance in their renal excretory function. The conclusions as to which abnormalities are due to renal insufficiency and which to extrarenal metabolic disturbances in the clinical symptom complex, we are pleased to call nephritis, are very incomplete and rest on evidence which has thus far only been slightly developed. It is necessary to bear the two possible factors, renal insufficiency and extrarenal disturbances, in mind especially when the subject of protein metabolism in nephritis is considered.

Utilization of Proteins in Nephritis.—The respiratory quotient in cases of nephritis does not vary from the normal; hence protein utilization may be considered as proceeding in the usual manner (Aub and DuBois, and Peabody, Meyer and DuBois). This is undoubtedly true in the

majority of cases. There are, however, certain symptoms and crises occurring in the course of some cases of nephritis that lead to the conclusion that, for brief periods at least, protein metabolism may be profoundly disturbed. These changes will be discussed under the headings of serum proteins, creatin and protein destruction. The significance of such perversions of protein metabolism is very difficult to decide. It is probable that all of them are the signs of a disturbance elsewhere in the body; in other words, that they are extrarenal in origin.

The Serum Proteins.—The serum proteins in nephritis have been investigated in regard to these points: *Variations in the quantity of the total proteins, albumin and globulin, and changes in the albumin: globulin ratio.* Some of the results obtained are contained in the following table:

TABLE 1

CHANGES OCCURRING IN THE SERUM PROTEINS IN NEPHRITIS ACCORDING TO VARIOUS OBSERVERS

Author—Diagnosis	Grams per 100 c.c. Serum						Percentage of Globulin	
	Total Protein		Albumin		Globulin			
	Highest	Lowest	Highest	Lowest	Highest	Lowest	Highest	Lowest
Rowe, A. H., 1916, 1917								
Normal	8.2	6.5	6.7	4.6	2.4	1.2	32	16
Chronic Nephritis without Uremia or Edema	7.9	6.1	6.1	3.6	2.5	1.3	40	21
Chronic Nephritis with Edema	5.3	3.8	3.9	1.9	2.0	1.4	50	26
Chronic Nephritis with Uremia	7.9	5.8	5.5	3.3	2.6	1.9	44	24
Kahn, M.								
Normal	8.5	6.8	5.4	4.4	3.2	2.3	40	31
Acute Nephritis	8.0	5.9	4.7	3.6	3.8	2.2	48	38
Chronic Interstitial Nephritis	8.7	6.5	5.7	3.9	3.8	2.6	41	34
Chronic Parenchymatous Nephritis	7.7	4.2	4.8	2.9	3.3	1.3	44	31
Epstein, A. A.	Average		Average		Average		Average	
Normal	7.4		4.7		2.7		37	
Chronic Interstitial Nephritis	6.7		4.3		2.4		36	
Chronic Parenchymatous Nephritis	3.9		0.5		3.5		89	

Rowe(*b*)(*c*) quotes former investigators and adds his own experience to show that in a general way in chronic diseases the blood serum protein and its albumin fraction are diminished while the globulin is increased; nephritis follows this rule. However, "No characteristic values for serum proteins which might aid in the clinical diagnosis of the type of kidney lesion were found." Nephritic edema proved to be accompanied by a low protein content in the serum; in cases of cardiac decompensation and edema, the serum proteins were not depressed to the same degree. Kahn (*c*) was unable to demonstrate a change of serum proteins in any form of

nephritis. Epstein(*b*) believed that in chronic interstitial nephritis the blood serum proteins were normal but that in chronic parenchymatous nephritis the serum protein was much diminished at the expense of the albumin fraction while the serum globulin was relatively, as well as actually, increased. In summary it may be said that, as the question stands to-day, there may be a slight diminution of the total serum protein and the serum albumin, accompanied by a slight rise in the serum globulin in chronic nephritis and that these changes may become very marked in the types of nephritis accompanied by edema. The whole problem is in a somewhat unsatisfactory state because the methods for the determination of albumin and globulin are not generally accepted and because the separation of these two forms of protein is based upon rather arbitrary grounds.

The *significance* of the above findings have been interpreted in widely divergent ways; none of them are as yet conclusive though they are of considerable importance in shaping future studies in regard to the nature and treatment of nephritis. It is believed that certain toxic substances cause changes similar to those recorded in nephritis. Thus Whipple and Cooke showed how similar variations occurred in the serum proteins of dogs with intestinal obstruction or closed intestinal loops; they believed this phenomenon to be brought about by a toxic proteose; the latter when isolated from the intestines and injected into animals was followed by exactly similar changes. Furthermore Hurwitz and Meyer in their studies on the serum globulins in bacterial infection and immunity have concluded that the increase of globulins occurring during the process of immunization is the result of the action of some toxic factor and is not a part of the process upon which the development of immunity depends. These two types of poisoning, intoxication from intestinal absorption, and from infection, are particularly stressed because they may both be associated with the production of nephritis. The deviation from the normal of the serum proteins of the nephritic may be an expression of the severity of a toxic effect upon which nephritis depends and not the direct result of the nephritis itself.

The reason for the association between the more evident changes that occur in the serum proteins of the edematous, as compared to the non-edematous, case of nephritis has been interpreted in various ways. Rowe rather inclines to the theory that a dilution of the blood serum, a hydremia, is responsible for the diminution of the proteins; this of course does not explain the relative and in some cases the absolute increase of the globulins, which, not only by Rowe but also by other authors, is ascribed to the effect of some unknown toxin. All the changes are accounted for by the latter theory by many observers. In view of what is now known of the action of proteose and bacterial poisons this assumption certainly has much in its favor. Epstein believes that the loss of albumin in the urine is

responsible for the diminution of the serum proteins; as a result of the lowered protein content of the blood, the osmotic pressure within it is decreased, and the flow of fluid is from the blood to the tissues, thus producing edema; by this author, as well, a toxic factor has to be resorted to to account for the disproportionately high globulin and other changes. The exact status of this question remains to be determined. It is very much

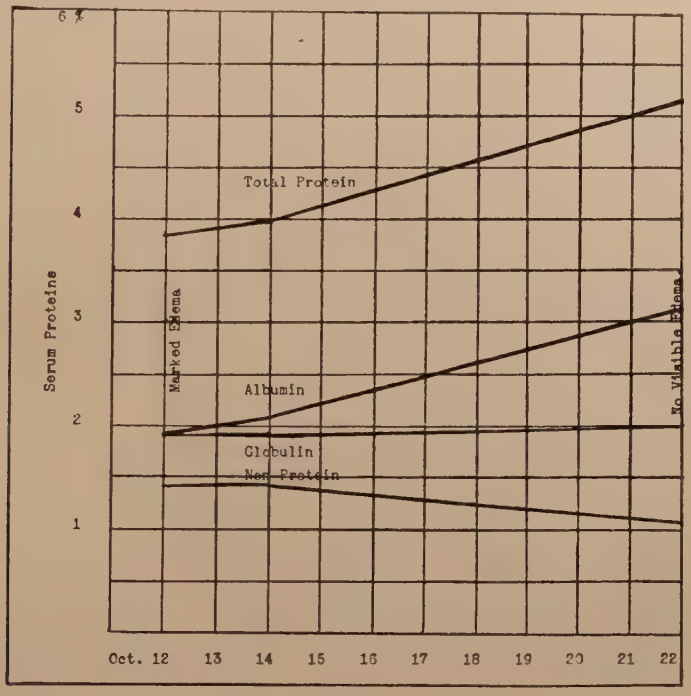


CHART 1

The low level of serum albumin and total serum proteins in severe nephritis with edema followed by a rise in these values with clinical improvement and loss of edema is shown. The separation of the albumin and globulin curves in this chart is a definite index of recovery, though the failure of the total proteins to reach a more normal value indicates a bad prognosis. (According to Rowe(*c*), 1917.)

in accord, however, with the conception that nephritis is a disease caused by some unknown extrarenal poison, to believe that such a toxic factor brings about changes in the serum proteins and at the same time is responsible for the lesions in the kidney.

As the edema clears up in nephritis the serum proteins tend to return to normal (Rowe(*c*), 1917). Within ten days after the severe stage has passed, the usual albumin: globulin ratio becomes established; the total protein content of the serum, although increased, may not be returned to a normal level. It is very interesting to note that the globulin values remain constant while those for albumin rise. Rowe, endorsing

previous investigators, believes that the inability of the total protein to reach a normal level means "internal edema," even though the "external edema" has completely disappeared and that this is also a manifestation of chronic intoxication present in nephritis. Such cases, with persistently low total and abnormal, albumin: globulin ratios have a poor prognosis. The chart from Rowe on page 317 illustrates these points.

The effect of feeding in restoring the serum proteins to normal is interesting from the therapeutic point of view. In the first place it must be borne in mind that proteins as such are not absorbed by the intestines, but only their derivatives, the amino acids, are. Hence feeding a particular albumin or globulin to restore these serum proteins to normal is a useless procedure. It was shown by Kerr, Hurwitz and Whipple(*a*)(*b*) that in dogs in whom the serum proteins had been lowered by plasmapharesis, that a more rapid regeneration occurred on a normal diet, especially a meat diet, than on fasting; under the most favorable circumstances it required five to eight days to regenerate the serum protein to normal. The effect of forcing protein food in case of chronic parenchymatous nephritis for a few days produced some increase in serum proteins, as shown in Table 2.

TABLE 2

EFFECT OF FEEDING PATIENTS SUFFERING WITH CHRONIC PARENCHYMATOUS NEPHRITIS A DIET HIGH IN PROTEINS. (Kahn)

	Total Serum Protein			
Before feeding	4.24	7.60	5.76	6.09
After feeding	5.27	7.75	6.12	6.37
	Serum Albumin			
Before feeding	2.93	4.26	3.75	4.14
After feeding	3.59	4.50	3.92	4.46
	Serum Globulin			
Before feeding	1.31	3.34	2.01	1.95
After feeding	1.68	3.25	2.20	1.91

Epstein(*b*) advocates not only a high protein diet, but also transfusions in his effort to restore the serum proteins to normal.

Summary.—In chronic nephritis the serum proteins may or may not be diminished; when such a change occurs it is brought about mainly through a reduction of the serum albumin; the serum globulin is nearly always relatively and at times absolutely increased. These abnormalities may be entirely or in part caused by the action of some extrarenal toxic substance of unknown nature. Such deviations from the normal occur most frequently in the types of nephritis associated with edema. The relation of the edema to the deviations from the normal of the blood pro-

teins is not at all clear. The investigations upon the subject of the serum proteins are replete with suggestions and possibilities but have thus far furnished very little else of importance.

The Non-Protein Nitrogen of the Blood and Tissues in Nephritis

The total non-protein nitrogen is made up of the sum of various substances derived from the digestion or disintegration of protein. The urea, uric acid, creatin, creatinin, amino acids, go to make up the major if not the entire amount of non-protein nitrogen. A certain fraction sometimes remains unaccounted for; this has been variously called the residue, rest or undetermined nitrogen. The author once asked a prominent biochemist as to what he thought this residue nitrogen was composed of. The response was very simple and direct: "The rest nitrogen represents the sum of the inaccuracies of the methods for the determination of the individual non-protein nitrogenous constituents; there is no undetermined nitrogen." This is a sweeping statement but it has more to be said for it than against it. In the first place, any one who has carried out many fairly complete analyses of the blood has encountered specimens in which the sum of the nitrogen derived from the non-protein nitrogenous constituents was greater than the total non-protein nitrogen value. In the second place, an accurate determination of the total non-protein nitrogen is impossible of attainment at the present time. This is not so much the fault of the methods as it is that it is not known at what point in the cleavage of protein into polypeptids, protein ceases to be protein and the non-protein nitrogen begins. The results obtained by chemical methods in vogue are consequently very different; in the preliminary step in these estimations, various coagulants are used to separate the protein from the non-protein fraction in the blood or tissue. If trichloracetic acid is employed, according to the method of Greenwald, the figures for non-protein nitrogen are considerably higher than when Folin's procedure, which resorts to methyl alcohol, is followed. Thus the figures for total non-protein nitrogen have comparative value only; the substances which the term represents are not definitely decided upon. The undetermined nitrogen for the present at least is a mythical substance and it does not seem wise to attribute any significance to it until it is more definitely established that it really exists. Inasmuch as the total non-protein nitrogen is made up of various nitrogenous constituents, it remains to determine the relation of these to one another in the blood and tissues as affected by nephritis.

As renal insufficiency develops, the uric acid is first retained in the blood, then the urea and, finally, the creatinin (see comparative value of uric acid, urea and creatinin in nephritis). The creatin may increase

TABLE 3

ANALYSIS OF NORMAL AND NEPHRITIC HUMAN MUSCLE. (Mosenthal, Hiller and Clausen, unpublished)

Diagnosis	Mg. per 100 Gm. of Muscle				
	Total N.P.N.	Urea N	Creatinin	Creatin	Amino Acid N
"Normal" from 13 carcinoma cases at operation.					
Maximal values ...	234	17	12	404	42
Minimal values	138	8	2	212	16
"Nephritis."					
Chronic nephritis..	657	242	11	287	27
Chronic nephritis and tubercular peritonitis	456	258	372		27
Bichlorid of mercury poisoning ..	422	9	8	422	43
Chronic nephritis..	411	168	18	345	22
Chronic nephritis..	386	232			
Chronic nephritis..	378	139	14	341	31
Chronic nephritis..	367	150	25	466	39
Chronic nephritis..	337	128	10	372	22
Chronic nephritis..	301	123			
Chronic nephritis..	284	63			
Chronic nephritis and sepsis.....	217	40	3	351	39
Acute exacerbation of chronic nephritis	214	24	4	488	20

towards the end of life in renal disease and presumably indicates the existence of accelerated protein destruction (see creatin in nephritis). The amino acids apparently remain unchanged throughout the course of the disease (see amino acids in nephritis). The greatest actual and proportional rise in the non-protein nitrogenous constituents in the blood occurs in the urea which under normal conditions constitutes about 50 per cent of the total non-protein nitrogen, while when the kidneys become unequal to fulfilling their task it goes up to between 80 and 90 per cent (see the relation of the urea to the total non-protein nitrogen of the blood in nephritis).

Bearing these facts concerning the blood in mind, the examination of the tissues becomes of importance. It is very essential to know whether by analyzing the blood an adequate conception if what is occurring in the other parts of the body may be obtained. The tissues might retain more or less of the non-protein nitrogenous materials than the blood. Foster(*b*) (1919) has shown that the total non-protein nitrogen in the tissues rises as it increases in the blood. From Table 3 it may be seen that the most marked rise occurs in the urea nitrogen, that there is a distinct increase in the creatinin and no change in the amino acid nitrogen. Thus the blood and tissue changes may be considered as paralleling each other very

TABLE 4

TISSUE ANALYSES IN A CASE OF CHRONIC INTERSTITIAL NEPHRITIS DYING OF UREMIA. (Myers and Fine, 1915)

Fluid or Tissue	Mg. per 100 Gm. or c.c.			
	Urea N	Creatinin	Creatin	Uric Acid
Blood	100	5.3	21.3	15.4
Ascitic fluid	100	6.0	15.3	18.0
Pleural fluid	100	6.3	11.3	16.7
Subcutaneous fluid	100	6.0	14.2	18.0
Spinal fluid	100	4.4	4.4	4.4
Pectoral muscle	125	6.8	324.0	8.0
Liver	116	5.3	50.5	10.0
Heart muscle	100	6.8	148.0	18.0
Spleen	115	7.8	26.7	12.6

closely. This is perhaps more strikingly brought out by the very complete set of analyses in a most interesting case of Myers and Fine (1915) (see Table 4). In this instance it may be noted that the urea, creatinin and uric acid are equally distributed except in the spinal fluid. As far as the urea is concerned such a result is only to be expected according to the work of Marshall and Davis. The creatin is in an entirely different relation than the other substances. Under normal conditions the highest creatin values are found in the muscle; this apparently is also true in nephritis; when the creatin is found in excess in the blood, it must be derived from the muscular tissue and has been regarded as a sign of an abnormal degree of protein disintegration. It would appear, therefore, that with the exception of the creatin, the non-protein nitrogenous constituents may be considered to be fairly evenly distributed throughout the body (excepting of course the fat, bones, cartilage and teeth) and that the values obtained by an analysis of the blood furnishes a true indication of what has occurred in the tissues.

The Urea of the Blood in Nephritis

The urea of the blood is the most used of the chemical tests resorted to for information regarding the retention of non-protein nitrogenous constituents in nephritis. This is because the estimation of this substance is more rapid, easier to carry out and possibly more accurate than is the case with the other compounds containing nitrogen. There is one other fact that must be kept in mind when the results for urea are valued. In large part the level of the urea in the blood is controlled by what are termed the exogenous factors; that is, the amount of protein food ingested will control it to some extent. This is not only an immediate effect, but one which lasts for some time. Thus in a group of 5 normal individuals, the blood urea nitrogen varied between 4.5 and 9.0 mg. per 100

c.c. when taken after a 12 hour fast following a two or three day period of low protein diet, whereas in the same group after they had eaten their customary food for several days, the blood urea nitrogen taken at a corresponding time (12 hours after the last meal) was considerably higher—9.8 to 15.9 mg. per 100 c.c. of blood. The substances, other than the urea, ordinarily determined in clinical tests, creatinin and uric acid, are not as markedly affected by dietetic therapy. How effective a low protein, high starch diet may be in reducing the non-protein nitrogen and urea in the blood may be gathered from Table 5. In this case of chronic nephritis the blood urea N was reduced from 126 mg. per 100 c.c. to 23. This can not be accomplished in every case of like severity; in milder instances it can be brought about very readily.

TABLE 5

THE UREA NITROGEN IS REDUCED MARKEDLY IN A CASE OF CHRONIC NEPHRITIS BY MEANS OF A LOW PROTEIN HIGH STARCH DIET

Date	Mg. per 100 c.c. Blood	
	Total N.P.N.	Urea N
October 14	145	126
" 21	123	103
" 29	66	49
November 16	95	63
" 23	79	55
" 31	41	30
December 6	32	23

It must be recognized that there are other influences besides the diet and renal efficiency that control the level of the blood urea. There are certain processes that may take place within the body,—protein destruction, water loss resulting in inspissation of the blood or dilution of the blood because of fluid retention which may modify the concentration of urea in the blood (Schwartz and McGill, Mosenthal(*a*), 1914). In the final analysis it must be faulty kidney action that is responsible for the urea retention; the factors considered above can only be regarded as contributory causes.

In chronic nephritis the blood urea rises slowly until a level of about 65 mg. of urea nitrogen per 100 c.c. has been reached; subsequently it is prone to increase with extreme rapidity (Mosenthal and Lewis). This is due in part to the marked effect produced by even slight diminution in renal function in kidneys that have already been extensively involved and in part due to an increase protein destruction that accompanies extreme oliguria or anuria, and a terminal state. In acute nephritis or the sudden onset of anuria the blood urea may rise with extreme rapidity. Thus in a dog after nephrectomy (Table 10) the blood urea nitrogen rose to 232 in four days. The figure of 351 mg. of urea nitrogen per 100 c.c. of

blood given in the case cited under protein destruction (Table 18) represents approximately as high a value as is usually reached in the cases with marked renal insufficiency.

Other aspects of the subject of urea in nephritis are taken up under the headings of the comparative value of uric acid, urea and creatinin in the blood in nephritis, the relation of the urea to the total non-protein nitrogen of the blood in nephritis, protein destruction in nephritis, renal function, and uremia.

The Relation of the Urea to the Total Non-Protein Nitrogen of the Blood in Nephritis

In nephritis, as well as in other conditions accompanied by renal insufficiency, when the non-protein nitrogen of the blood rises it is accompanied by a disproportionately rapid increase of the blood urea. This results in a rise of the percentage figures for the urea nitrogen of the total non-protein nitrogen (Hohlweg, Obermayer and Popper, Farr and Austin, Tileston and Comfort(*a*)(*b*), Mosenthal and Hiller). The actual percentage obtained will vary somewhat according to which method is employed to determine the non-protein nitrogen. The different coagulants used to separate the protein from the non-protein part of the blood precipitate unequal fractions. Thus, the trichloracetic method of Greenwald yields considerably higher results for the non-protein nitrogen than the methyl alcohol method of Folin. The following figures apply to results obtained with the alcohol method of Folin.

The normal human being usually metabolizes protein in such a manner that approximately 80 per cent of the nitrogen set free in the blood is in the form of urea. The selective action of the kidney maintains the urea nitrogen at a level of 50 per cent or less of the total non-protein nitrogen of the blood. An impairment of renal function, even of very slight degree, may result in an increase in the percentage of urea nitrogen. The following table gives an approximation of what is to be expected in this regard.

TABLE 6

APPROXIMATE PERCENTAGES OF UREA N AS TOTAL NON-PROTEIN NITROGEN INCREASES IN THE BLOOD. (Mosenthal and Hiller.)

TOTAL NON-PROTEIN NITROGEN Mgm. per 100 c.c. Blood	APPROXIMATE UREA NITROGEN Percentage of Total Non-protein Nitrogen
30 or less	55
31-60	65
61 or more	75 or higher

In patients whose clinical condition does not vary very appreciably, the percentage of urea nitrogen remains constant whether the total non-

protein nitrogen is high or low. This fact makes it feasible to differentiate the cases with impaired renal function from normal individuals, when the non-protein nitrogen is not raised. The data in Table 7 show how the percentage of urea nitrogen remains fairly constant regardless of the level of the total non-protein nitrogen.

TABLE 7

DATA FROM A CASE OF CHRONIC NEPHRITIS WITH A CONSTANTLY HIGH PERCENTAGE OF UREA N REGARDLESS OF WHETHER THE TOTAL NON-PROTEIN NITROGEN IS HIGH OR LOW. (Mosenthal and Hiller.)

Date	Milligrams per 100 c.c. Blood		Per Cent Urea N of Total Non-protein Nitrogen
	Total Non-protein Nitrogen	Urea N	
October 8	125	99	79
October 14	145	126	87
October 21	123	103	84
October 29	66	49	74
November 16	95	63	66
November 23	79	55	70
November 31	41	30	73
December 6	32	23	72
December 10	36	26	72
January 12	68	52	76
January 25	63	45	71
February 19	194	153	79
February 23	192	149	78
March 3	216	170	79
March 9	205	161	79
March 10	210	174	83
March 11	212	175	83
March 15	210	168	80
March 19	196	144	74
March 20	210	168	80
March 21	222	175	79

Cases with acute renal conditions show a high percentage of the urea nitrogen of the blood which returns to normal as convalescence occurs. This is well illustrated in Table 8.

TABLE 8

DATA FROM A CASE OF ACUTE NEPHRITIS, DEMONSTRATING THE CHANGE FROM A HIGH TO A NORMAL PERCENTAGE OF UREA NITROGEN DURING CONVALESCENCE. (Mosenthal and Hiller.)

Date	Milligrams per 100 c.c. Blood		Per Cent Urea N of Total Non-protein Nitrogen
	Total Non-protein Nitrogen	Urea N	
October 27	60	45	75
November 1	57	36	63
November 3	49	27	55
November 30	32	22	69
December 6	19	12	63
December 8	14	9	64
December 13	16	9	56
December 20	18	8	44

The disproportionately rapid accumulation of urea in the blood is a phenomenon characteristic not only of nephritis but of any condition in which renal insufficiency exists. Thus in a case of polycystic kidneys (Table 9) and in a dog upon whom double nephrectomy had been performed (Table 10) the same rise in the percentage of urea nitrogen may be noted.

TABLE 9

DATA FROM A CASE OF CONGENITAL POLYCYSTIC KIDNEYS. THERE IS A HIGH PERCENTAGE OF UREA N IN THIS PATIENT WHO MAY BE CONSIDERED TO EXHIBIT A TYPE OF RENAL INSUFFICIENCY NOT COMPLICATED BY ABNORMAL METABOLIC CONDITIONS IN ANY OTHER TISSUES. (Mosenthal and Hiller.)

Date	Milligrams per 100 c.c. Blood		Per Cent Urea N of Total Non-protein Nitrogen
	Total Non-protein Nitrogen	Urea N	
February 6	86	70	81
February 10	112	90	80
February 19	86	69	80
March 2	88	62	70

TABLE 10

DATA FROM A NEPHRECTOMIZED DOG. THE PERCENTAGE OF THE UREA N RAPIDLY RISES. (Mosenthal and Hiller.)

Date	Milligrams per 100 c.c. Blood		Per Cent Urea N of Total Non-protein Nitrogen	Remarks
	Total Non-protein Nitrogen	Urea N		
December 6	23	10	44	Blood obtained at time of nephrectomy
December 7	78	54	69	
December 8	138	119	86	
December 9	205	166	81	
December 10	275	232	84	Died

It may be concluded that under normal conditions the urea nitrogen composes about 80 per cent of the non-protein nitrogen in the urine and about 50 per cent of that in the blood. The selective excretory action of the kidney maintains these relations; when renal function becomes impaired, from any cause whatsoever, the percentage of urea nitrogen in the blood, approximating that present in the urine, rises, and is maintained at the higher level whether the total non-protein nitrogen of the blood is high or low; if normal renal function is again attained, as occurs in many cases of acute nephritis, the blood urea drops to its usual level. This percentage relation of the urea nitrogen to the total non-protein nitrogen may be advantageously utilized as a measure of renal function. The relation of the urea to the other non-protein nitrogenous constituents of the blood will be taken up in the succeeding chapters.

Creatinin in Nephritis

It was demonstrated almost simultaneously by Neubauer(*e*), Folin and Denis, and Myers and Fine(*b*)(1913), that an increase of blood creatinin occurred in certain types of nephritis. According to Myers and Lough, creatinin rises above 2.5 mg. per 100 c.c. of blood only in conditions associated with renal insufficiency; 2.5 to 3 mg. may be viewed with suspicion, 3.0 to 5 mg. indicate a decided retention of the nitrogenous waste substances, while an amount above 5 mg. portends an early fatal termination. Myers and Kilian(*b*) note that in exceptional instances such patients may live for one year. The author has seen several similar cases. The above applies to chronic nephritis. In acute nephritis and bichlorid of mercury poisoning such high levels of blood creatinin are not necessarily significant of a fatal prognosis inasmuch as if the kidney again secretes an adequate quantity of urine a complete recovery may ensue. In chronic nephritis, the blood creatinin has been observed to be higher than 30 mg. per 100 c.c. (Chace and Myers(*b*), 1916). In those cases of nephritis in which no renal insufficiency exists the creatinin does not increase in the blood. This applies particularly to certain cases of acute or chronic nephritis with albuminuria in which the illness may be very severe and yet no retention of creatinin or other nitrogenous waste products occurs unless the oliguria becomes marked or anuria supervenes.

Under normal conditions, the creatinin content of voluntary muscle is two or three times as great as that of the blood. The subsequent table (11) shows the normal values for the creatinin content of human voluntary muscle to vary between 2 and 12 mg. per 100 gm. of tissue while the blood creatinin usually varies between and 1 and 2 mg. and only in isolated instances does it rise as high as 2.5 or 3 mg. In uremia the blood creatinin accumulates faster than it does in the muscle (Myers and Fine (*d*), 1915). There are comparatively few investigations concerning the creatinin content of muscle in nephritis.

It is evident that in nephritis there may be an increase in the muscular creatinin which may assume considerable proportions. It is probable that the creatinin in this tissue has no more significance than it has in the blood, namely, retention because of renal insufficiency. The two cases of acute nephritis cited in the table show no increase, whereas in the instances of chronic nephritis the creatinin rises as high as 25 mg. per 100 gm. Presumably there are cases of acute nephritis in which the muscle creatinin would be increased just as there are instances of acute nephritis with a high blood creatinin, while in many it does not rise above the normal level. The findings depend entirely upon the absence or presence of renal insufficiency.

All the facts thus far recorded agree with the view of a number of ob-

TABLE 11

CREATININ OF HUMAN VOLUNTARY MUSCLE IN NEPHRITIS

Creatinin Mg. per 100 Gm. Muscle		Remarks	Author
Normal	Nephritis		
11.5	10.0	Acute nephritis Death in coma	Shaffer
2.6 – 5.7	6.8 18.1	Interstitial nephritis uremia	Myers & Fine (1915)
2. – 12.	10 11 14 18 25 4	Chronic nephritis " " " " " " " " Acute exacerbation Chronic nephritis	Mosenthal, Hiller & Clausen (Unpublished)

servers and championed by Myers and Fine(*d*)(1915) that creatinin is probably formed from creatin unless ingested as preformed creatinin. Furthermore, it may be concluded that creatinin, when once formed, undergoes no chemical transformation but remains in the body until excreted by the kidneys.

It is probable that creatinin in itself has little or no toxic effect. This is demonstrated by the absence of untoward symptoms in the numerous experiments on man and animals in which creatinin has been injected or ingested. Myers and Killian(*b*) believe that it may be the cause of uremia. This, however, is only based upon theoretical grounds and is contradicted by the evidence cited in the same paper that some cases, with a high blood creatinin, survive a considerable length of time. A rise in the blood creatinin certainly must be looked upon as a grave sign of renal insufficiency. The kidney eliminates creatinin with great ease and this substance is therefore among the last of the end products of protein metabolism to be increased in the blood (see section on relation of uric acid, urea and creatinin in the blood in nephritis). An augmentation of creatinin in the blood is, however, only a signal of marked renal insufficiency; in itself it has no further significance. The actual cause of uremia, brought on by retention of waste products, can not be attributed to creatinin but is to be sought in other substances which are simultaneously held back by the damaged kidney.

Creatin in Nephritis

Not much attention has been paid to the metabolism of creatin in nephritis. The observations which are at hand indicate that the estima-

tion of creatin in the blood has no great clinical value at present, but may be of considerable importance in determining the course of protein metabolism in this disease.

Under normal conditions (excepting in children, and at times in women) there is no creatin in the urine while the creatin in the blood attains a level of 3.5 to 6 mg. per 100 c.c. (Folin and Wu). The greater portion of the blood creatin is contained in the corpuscles; only a slight amount is present in the plasma (Hunter and Campbell). It is the quantity of the creatin in the plasma, according to Hunter and Campbell, which determines the presence or absence of creatinuria. Whenever the plasma creatin (uncorrected figures) is lower than 1.4 mg. per 100 c.c., the urine is creatin free; when it is above 3.2 mg., creatinuria appears. The term "uncorrected figures" applies to results obtained with Folin's original method, which is not reliable for the determination of blood creatin, but furnishes data which are about double the true value; however, until other observations are forthcoming they may be accepted as having a "provisional validity." All the figures given in this section were obtained by this method.

Two deductions of considerable significance may be made from the above facts. First, that the absence or presence of creatin in the urine is largely a matter of the level of the kidney threshold to this substance in the plasma and not, as has been frequently taken for granted, solely a problem of metabolism; second, that, inasmuch as the creatin in the blood is not eliminated, the body must possess the power of destroying it. An accumulation of creatin in the blood would therefore be due to a diminished ability of the body to change creatin chemically or to an increased production of creatin. The former probably does not take place, and the latter is much the more likely occurrence. An increased formation of creatin is now generally acknowledged to be associated with the destruction of muscle protein (see section on creatin metabolism). A rise in the blood creatin in nephritis would therefore indicate an accelerated disintegration of protein, especially of muscle protein.

The few available observations indicate that the blood creatin rises when renal insufficiency exists. Myers and Fine (*c*)(1915) found the creatin content of nephritic blood to be as high as 31.4 mg. per 100 gm.; in the author's series it reached the level of 26.9 mg. These are terminal cases. Earlier in the disease, it is usual for the blood creatin to show increments of less marked degree (see table 12). If the present theories of creatin metabolism are correct, these facts indicate that a destruction of protein commonly occurs in nephritis and, to a less extent, in other diseases associated with renal insufficiency. The amount of protein catabolism above the normal is too slight to be detected by calorimetric determinations (see section on the utilization of proteins in nephritis). It does not necessarily follow that this slight increase in protein catabolism

TABLE 12

CREATIN VALUES OF BLOOD COMPARED WITH THOSE OF SOME OF THE OTHER NON-PROTEIN NITROGENOUS CONSTITUENTS. THE INCREASE IN BLOOD CREATIN OCCURS ONLY WHEN RENAL INSUFFICIENCY IS FAR ADVANCED; IT DOES NOT PARALLEL ANY OF THE OTHER SUBSTANCES. (Mosenthal, Hiller and Clausen, unpublished)

Diagnosis	Mg. per 100 c.c. Blood			
	Creatin	Creatinin	Urea N	Uric Acid
Normal in this series	3.5-4.8	1.7-2.3	4.5-15.9	1.0-2.6
Essential Hypertension	4.7	1.5	16	1.7
Chronic Nephritis	4.7	1.2	53	3.2
" "	5.1	16.7	124	5.3
" "	7.3	1.4	21	3.4
" "	9.2	12.9	134	2.7
" "	12.4	6.8	144	2.4
" "	14.9	8.1	164	4.1
" "	26.9	18.5	176	5.3
Carcinoma of the Cervix, Urethral Obstruction	9.4	9.3	147	2.8
Polycystic Kidney	8.2	8.0	90	6.2
Bladder Paralysis, Tabes Dorsalis	8.4	4.4	70	2.9

is due to nephritis; it may be caused by the partial or complete starvation which these patients are unavoidably subjected to.

In the voluntary muscle, creatin does not rise as renal insufficiency develops. This may be seen in Table 13. The figures for urea N in the parallel column indicate that the excretory function of the kidney has been definitely curtailed and yet the creatin values are not always above normal. In those instances in which the creatin is raised the urea N is not necessarily increased. These observations bear out what has been noted in the preceding discussion of the significance of creatin in the blood, namely, that the rise in blood creatin, while associated with renal insufficiency, is not caused by it, but is brought about by protein disintegration. The comparatively low creatin content of nephritic

TABLE 13

CREATIN CONTENT OF MUSCLE IN NEPHRITIS. IT DOES NOT USUALLY RISE ABOVE THE NORMAL LEVEL, EVEN THOUGH THERE IS MARKED RENAL INSUFFICIENCY AS INDICATED BY THE FIGURES FOR UREA N. (Mosenthal, Hiller and Clausen, unpublished.)

Diagnosis	Mg. per 100 gm. Muscle	
	Creatin	Urea N
Normal in this series	212–404	8–17
Chronic Nephritis	287	242
Chronic Nephritis	341	139
Chronic Nephritis	345	168
Chronic Nephritis and Sepsis	351	40
Chronic Nephritis	372	128
Bichlorid of Mercury Poison	422	9
Chronic Nephritis	466	150
Acute Exacerbation of Chronic Nephritis	488	24

muscle and the increased amounts of creatin in the blood, indicate a liberation of creatin from the muscle which passes into the blood, in other words, a disintegration of muscle tissue. Attention should again be called to the probability that the complete or partial starvation characteristic of the advanced nephritic state may be responsible for such an increased protein katabolism and that nephritis in itself may not be the cause of the protein disintegration.

The Comparative Value of Uric Acid, Urea and Creatinin in the Blood in Nephritis

Myers and his associates have elaborated certain relationships of these substances in the blood of nephritics that have proved to be of considerable value in judging of the clinical progress of renal insufficiency (Chace and Myers(*b*), 1916). A high uric acid is often present when there are no other signs of retention. Bauman, Hausmann, Davis and Stevens noticed the increase of uric acid content of the blood as one of the earliest signs of renal insufficiency. Creatinin, on the other hand, rises above the normal values in the blood only in the terminal stages of nephritis. In making a comparison of these non-protein nitrogenous substances, in the blood and urine, it was found that the kidney could concentrate the creatinin one hundred times, the urea eighty times and the uric acid only about twenty times. From these facts, it is evident that of these three substances, creatinin is most readily eliminated by the kidney and uric acid with the greatest difficulty. This makes it clear why uric acid is first retained, then urea, and finally creatinin. While an increase in uric acid indicates only a slight degree of renal insufficiency, a rise in the blood creatinin is the signal of marked deficiency in kidney function. Grouping cases of nephritis according to their severity a "staircase like" picture is obtained of the increments of uric acid, urea and creatinin in the blood. This is shown in Table 14.

The above relationships are characteristic of the majority of cases of nephritis. If uric acid only is increased in the blood, it must be borne in mind that gout, leukemia, or other metabolic disturbance and not a renal insufficiency, may be the cause for such a change. It is frequently taken for granted that a rise of the blood uric acid indicates either gout or impairment of renal function. This is an unwarranted assumption, as there are many instances of uric acidemia in which neither cause plays a part. Until more is known concerning such conditions the figures for blood uric acid must be interpreted conservatively. Dietary restrictions may also be responsible for some current disturbances in these ratios. Inasmuch as uric acid, and especially urea, are largely of exogenous origin, and creatinin of endogenous, it follows that a low protein diet may re-

duce the uric acid and urea figures in the blood to a normal level while the creatinin remains high.

TABLE 14

URIC ACID, UREA NITROGEN AND CREATININ OF BLOOD IN NEPHRITIS. (Chace and Myers) (*b*)

Diagnosis	Condition	Mg. per 100 c.c. of Blood *			Phthalein 2 Hrs., per Cent.
		Uric Acid	Urea N	Creatinin	
Pulmonary tuberculosis	Unchanged	6.5	16	2.7	58
Pericarditis	Unchanged	5.6	13	2.1	45
Interstitial nephritis	Unchanged	5.5	12	2.5	37
Diffuse nephritis	Unchanged	9.6	19	2.4	45
Early interstitial nephritis	Unchanged	9.5	25	2.5	13
Early interstitial nephritis	Unchanged	6.6	24	3.3	26
Early interstitial nephritis	Unchanged	8.7	20	3.6	20
Early interstitial nephritis	Unchanged	6.3	31	2.0	23
Moderately severe chronic interstitial nephritis	Improved	8.0	80	4.8	0
		4.9	17	2.9	10
Moderately severe chronic diffuse nephritis	Improved	8.3	72	3.2	25
		5.3	21	1.9	43
Moderately severe chronic diffuse nephritis	Improved	9.5	44	3.5	38
		2.5	19	1.9	52
Typical fatal case of chronic interstitial nephritis	Died	22.4	236	16.7	0
Typical fatal case of chronic interstitial nephritis	Died	15.0	240	20.5	2-3
Typical fatal case of chronic interstitial nephritis	Died	14.3	263	22.2	0
Typical fatal case of chronic interstitial nephritis	Died	8.7	144	11.0	Trace

* Normal findings: uric acid from 2 to 3 mg.; urea nitrogen, from 12 to 15 mg.; creatinin, from 1 to 2.5 mg. per 100 c.c.

Amino Acids in Nephritis

It has been established largely through the efforts of Van Slyke(*d*) and his collaborators that the proteins, after being separated into their constituent amino acids in the intestine, pass to the liver in the portal circulation where many of them are changed to urea; some of them are absorbed and stored in the liver and others pass on to the muscles to be stored there. It has become apparent that the amino acids, as they occur in the tissues, are substances that are either destined for the synthesis of protein or represent waste material resulting from protein catabolism. When protein distintegration does occur, the amino acids are not necessarily increased in the blood (Whipple and Van Slyke(*a*)). In a recent study of acute yellow atrophy, Stadie and Van Slyke concluded that under ordinary circumstances the liver can deaminize any amount of amino acids present in the circulation, even if there is an extensive breakdown of protein material, and that abnormal amounts of amino acids result only when the destruction of the liver cells is almost complete. These conclusions would point to lesions in the liver in case the amino acids increased

in the blood and tissues in nephritis. Bock found such an increase. (Normal amino acid content of the blood, 6.13 to 7.90 mg. per 100 c.c., high

TABLE 15

AMINO ACID CONTENT OF THE BLOOD IN NEPHRITIS AND OTHER FORMS OF RENAL INSUFFICIENCY. THE FIGURES FOR UREA NITROGEN ARE TABULATED TO FURNISH SOME CONCEPTION OF THE DEGREE OF IMPAIRMENT OF KIDNEY FUNCTION. THE AMINO ACID NITROGEN RARELY EXCEEDS THE NORMAL LEVEL

Diagnosis	Mg. per 100 c.c. Blood	
	Urea Nitrogen	Amino Acid Nitrogen
Upper normal limit in control cases with same methods	16	10.0
Chronic diffuse (parenchymatous) nephritis	21	5.3
" " " "	45	4.4
" " " "	66	9.4
" " " "	89	8.0
" " " "	110	6.6
" " " "	124	12.5
" " " "	164	9.7
" " " "	176	7.2
Arteriosclerosis of the kidney	53	8.0
" " " "	132	11.8
" " " "	134	4.8
Renal insufficiency from other causes than nephritis :		
Polycystic kidney	69	10.5
" "	90	10.4
Tabes and bladder paralysis	70	5.3
Carcinoma, urethral obstruction	147	7.0

values in cases of nephritis 15.10, 17.50, 29.98). There have been comparatively few investigations of this matter; the author's results (Tables 15 and 16) would indicate that such a rise of amino acid nitrogen does

TABLE 16

AMINO ACID CONTENT OF MUSCLE IN NEPHRITIS. THE FIGURES FOR UREA NITROGEN ARE TABULATED TO FURNISH SOME CONCEPTION OF THE DEGREE OF IMPAIRMENT OF KIDNEY FUNCTION. THE AMINO ACID NITROGEN DOES NOT EXCEED THE NORMAL LEVEL

Diagnosis	Mg. per 100 c.c. Muscle	
	Urea Nitrogen	Amino Acid Nitrogen
Upper normal limit in control cases (healthy muscle obtained in operations for carcinoma of breast, etc.) with same method	25	42
Chronic nephritis	242	27
" "	150	39
" "	168	22
" "	128	22
" "	139	31
Chronic nephritis and sepsis	40	39
Acute exacerbation of chronic nephritis	24	20
Chronic nephritis and tubercular peritonitis	258	27
Bichlorid of mercury poisoning	9	43

not usually occur either in the blood or tissues, even when there is marked renal insufficiency as shown by the increase in the urea content. Woods obtained similar analyses, excepting a case suffering with complete anuria for 5 days, in which the amino acid nitrogen reached a level of 16.32 mg.

It is to be expected that the amino acids in the blood and tissues should remain at a normal level, inasmuch as, if those acids ordinarily destined to be excreted in the urine are retained because of renal insufficiency, the liver would transform them to urea, and they would thus lose their chemical identity. It seems probable, therefore, that the amino acid content of the blood and muscles remains normal in nearly all cases of nephritis. The few cases reported in which the amino acid nitrogen in the blood is increased remain to be confirmed. It is possible that the liver can not deaminize certain amino acids very readily and if these occur in larger amounts than usual, they may accumulate in the blood and tissues if the kidney is unable to eliminate them.

The Nitrogen Balance in Nephritis

Before the advent of blood chemistry, the determination of the nitrogen balance in nephritis was regarded as one of the most reliable tests of the ability of the kidney to eliminate this substance. This in a measure is still true, though there are certain conditions that limit the value of this procedure. For the proper interpretation of a nitrogen balance, three factors must be known:

1. The nitrogen intake.
2. The nitrogen output in the urine and feces.
3. The course of intermediary nitrogenous metabolism.

The first two of these demands are readily fulfilled; the third is vague in its requirements and no definite standards can be established for it; consequently much must be left to the judgment of the clinician or investigator. However, by the proper application of the figures for nonprotein nitrogen or urea in the blood, many of the facts that were formerly left to chance may be accorded their true meaning.

Besides the simple equation between intake and output, there are some processes that may cause a discrepancy in the nitrogen balance which makes it somewhat difficult to be certain of the actual meaning of this procedure. The tendency has been to attribute a lag of nitrogen elimination to renal insufficiency in every instance; however, if the tissues incorporate the ingested nitrogen, that is, assimilate it, a positive nitrogen balance results which may be due to physiological processes and not to pathological changes in the kidney (see Table 17). An augmented protein destruction or a marked loss of water may serve to raise the level

of urea or non-protein nitrogen in the blood; these must be regarded as contributing factors towards changes in the blood; in the last analysis

TABLE 17

THE NITROGEN BALANCE FOR THE WHOLE PERIOD IS + 69.1 GM. THE THEORETICAL VALUE OF THE NON-PROTEIN NITROGEN OF THE BLOOD, CALCULATING FROM THE FIRST OBSERVATION OF 29 MG. PER 100 C.C., SHOULD BE 119 MG., PROVIDED THE RETAINED NITROGEN WERE CIRCULATING AS WASTE NITROGEN; THE ACTUAL VALUE IS 27 MG. (Mosenthal and Richards)

Nitrogen Gm. in 24 Hours					Non-protein Nitrogen of the Blood Mg. per 100 c.c.
Urine	Feces	Total Output	Intake	Balance	
11.15	1.46	12.61	11.56	— 1.05	29
8.57	1.31	9.88	14.08	+ 4.20	
13.21	0	13.21	13.23	+ 0.02	
12.79	3.28	16.07	15.11	— 0.96	
6.62	1.96	8.58	19.09	+10.51	
7.25	2.75	10.00	19.91	+ 9.91	
11.00	0	11.00	13.93	+ 2.93	
10.46	2.53	12.99	19.89	+ 6.90	
13.55	1.71	15.36	19.12	+ 3.76	
12.26	1.91	14.17	11.99	— 2.18	26
12.65	1.80	14.45	14.50	+ 0.05	
12.76	0.97	13.73	15.15	+ 1.42	
13.80	0	13.80	17.56	+ 3.76	
13.70	2.94	16.64	13.28	— 3.36	
15.48	0	15.48	14.35	— 1.13	
15.60	4.34	19.94	21.96	+ 2.04	
16.46	0	16.46	18.33	+ 1.87	
14.88	4.43	19.31	24.86	+ 5.55	
14.90	4.45	19.35	24.39	+ 5.04	
12.59	2.78	15.37	23.09	+ 7.72	
13.67	3.42	17.09	24.93	+ 7.84	
13.96	0	13.96	21.91	+ 7.95	
14.85	5.46	20.31	16.61	— 3.70	27

of course it is the ability of the kidney to handle the waste products presented to it that is the controlling element in regulating the level of urinary excretory products in the circulation (Mosenthal(*a*), 1914, Mosenthal and Richards).

By application of biochemical facts recently ascertained, the fate of ingested nitrogen may at least be approximated from blood determinations. It is known from the work of Marshall and Davis that urea is evenly distributed throughout the body, except in certain tissues, as the fat, bone, cartilage, teeth, outer layers of the skin, etc., which do not take up urea. Since the greater part of the nitrogen of the food—approximately 85 per cent—is excreted as urea on a moderately high nitrogenous diet, a substantial increase in the non-protein nitrogen of the blood would be expected if the kidneys did not eliminate this substance sufficiently rapidly to keep pace with its production. It is at the present time not accurately known how the other nitrogenous products destined for urinary excretion are distributed in the body. Many of these are evidently stored in the tissues in much greater concentration than they are found in

the blood. However, these materials are probably being held for further use in the body and may be considered in a vastly different light from those which are to be excreted. For the purposes of determining the theoretical values of the non-protein nitrogen of the blood in cases in which it was supposed that the nitrogen output should have equaled the intake, the total quantity of retained nitrogen has been assumed to be equally distributed in the body. From the figures given by Marshall and Davis it is found that in an individual weighing 70 kilos the retention of 30 grams of urea is equivalent to a rise of 40 mg. per 100 c.c. in the urea of the blood. Applying the same principles to the total non-protein nitrogenous products which are supposed to be excreted by the kidneys, it is seen that for every gram of nitrogen retained, the non-protein nitrogen of the blood should be increased 1.33 mg. per 100 c.c. The same figures could be applied, for similar reason, to increments in the urea nitrogen of the blood.

How misleading a nitrogen balance study may be can be observed in Table 17. This case of nephritis retained considerable nitrogen, 69 gm. in 23 days, or 3 gm. a day; however, this is not due to faulty action on the part of the kidney, but evidently is brought about because the tissues are assimilating the nitrogenous material offered them. This is proved by the fact that the non-protein nitrogen in the blood did not rise, but remained at a constant level.

As is shown in the section on renal function, it is not possible to judge of the extent of kidney involvement according to its ability to excrete nitrogen or any other substance. A slight injury of the kidneys may produce an irritability ("hyposthenuria") and overactivity of these organs and thus result in over- rather than undersecretion. Furthermore, the level of the blood nitrogen or urea has to be taken into account. If these substances are raised they furnish a greater stimulus to the kidney and greater quantities will be excreted than if they are normal in amount. This is made evident in the discussion on the cofficient of urea excretion. Under these circumstances the curious condition may exist in which the output of nitrogen equals the intake and yet the kidney's ability to eliminate this substance may be markedly impaired as evinced by the very high values for blood urea or total non-protein nitrogen.

That different degrees of renal injury, even when due to the same toxic substance, do not result in a constant effect upon kidney activity, may be seen in Chart 2. Three dogs poisoned by uranium each showed a different state, as far as elimination of nitrogen was concerned. One excreted this material in normal amounts, another in diminished quantities, and in a third the elimination was distinctly greater than during the control periods. Similar observations have been made many times in nephritis. Hyposthenuria, protein destruction, polyuria, inspissation

of the blood, the level of the non-protein nitrogen of the blood and marked renal injury all play their part in producing these various pictures.

It becomes clear from what has been said, that the determination of nitrogen in the urine has but a limited applicability to measuring the efficiency of renal function. A single determination of the non-protein nitrogenous constituents of the blood furnishes a much clearer conception

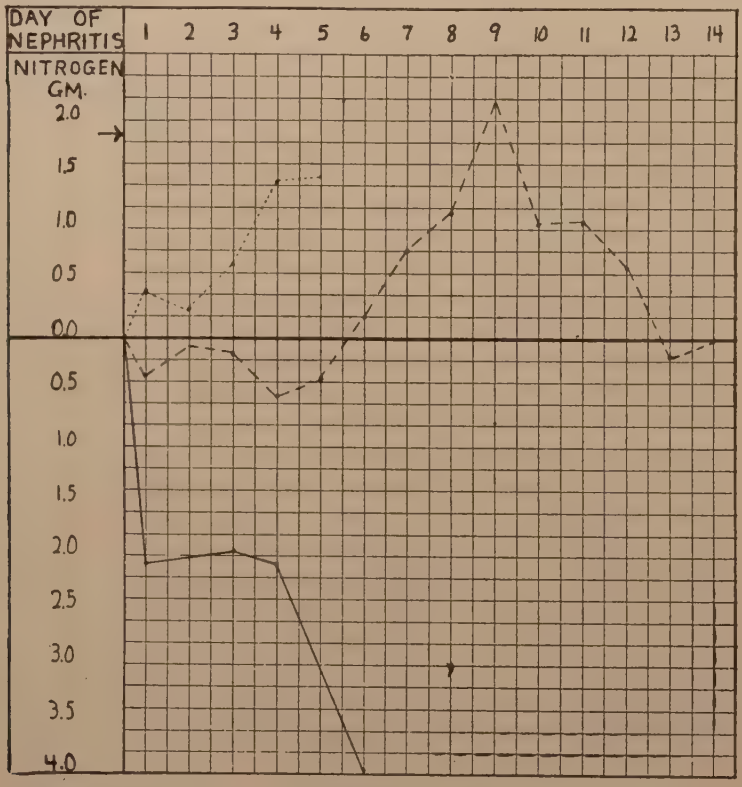


CHART 2

Comparative curves of excretion of urinary nitrogen as compared with amount of nitrogen of the control periods in experimental uranium nephritis in dogs. Various types of elimination are shown. Arrow indicates time of uranium injection. Solid line across chart indicates level of urinary nitrogen during control period; curves above line, excess of excretion; below, retention. Line of dashes, Dog 10; dotted line, Dog 23; solid line Dog 25. (Mosenthal(*a*), 1914.)

of how the kidney is acting (see comparative value, uric acid, urea and creatinin in the blood in nephritis). If the urea is low, the coefficient of urea excretion or the percentage relation of the urea nitrogen to the non-protein nitrogen will indicate the ability of the kidney to excrete the end products of protein metabolism. (See the relation of the urea to the total non-protein nitrogen of the blood in nephritis.) It is really a great satisfaction to realize that a single determination of non-protein nitrogen or

urea in the blood is a measure of the nitrogen balance for that individual's entire life. It is making a big effort with very little result to perform all the steps required to test out the nitrogen balance, by the older procedure of measuring intake and output over several days when a single chemical procedure furnishes a much more accurate answer.

Possibly more space than necessary has been devoted to the discussion of the nitrogen balance in nephritis than is warranted. However, it may be of some value to understand the various pitfalls which the clinician who employs this method of observation may meet with, and furthermore, it is very important to make clear that blood chemistry has to a very great extent supplanted quantitative urine analyses. This one phase of urinary examination has been gone into in some detail so as to make the points brought forward clear; other aspects of quantitative urine analyses, as far as they are of importance to metabolism, will be taken up under renal function, but the stress that was formerly accorded the 24 hour balance of all the materials normally found in the urine is out of place, since, just as for nitrogen, the examination of the blood furnishes a much better criterion than the comparative estimation of intake and output.

Protein Destruction in Nephritis

It has been assumed for some time that protein destruction plays a part in Bright's disease. Senator believed that it occurred in uremia; Von Noorden and Richter each reported one case in which an excessive elimination of nitrogen as compared to the food intake was supposed to indicate that a disintegration of body tissue had taken place. No one was really in a position to be certain of his ground in regard to this problem until the microchemical methods were successfully applied to the determination of the non-protein nitrogen of the blood. With this added source of information, not only can the intake and output of nitrogen be estimated, but also the course of intermediate metabolism (see section on the nitrogen balance in nephritis) can be gauged. All of these three factors must necessarily be known if occurrence of protein destruction is to be definitely demonstrated.

It is interesting to note that protein destruction may occur in a variety of conditions. Intestinal obstruction, the presence of a closed intestinal loop, the injection of toxic proteose, may all bring it about (Whipple and Cooke). In these instances a heaping up of nitrogen in the blood, while its excretion in the urine is increased, can only be explained on the basis of an augmented protein catabolism. Plasmaphoresis entails a similar injury to body protein (Kerr, Hurwitz and Whipple(*a*)(*b*)). This is supposedly due to marked dilution of the plasma. It suggests the possibility that the same phenomenon may take place if edema comes on very rapidly.

A disintegration of protein is at times present in diabetes mellitus (Allen and Du Bois). In the infectious disease it is generally appreciated that destruction of protein is the rule. Its intensity apparently depends upon the particular toxic causative agent and not upon any single symptom such as fever. For instance, the process is much more marked in typhoid fever than it is in tuberculosis. A study which has particular application to the subject in hand, is that of Matz. He studied the blood chemistry of cases of bronchopneumonia during an influenza epidemic at Camp Travis, Texas; apparently kidney involvement in his cases played no rôle, and yet in some instances the urea nitrogen rose as high as 148 mg. per 100 c.c. of blood, the creatinin 5 mg. and the uric acid 11.8 mg. It is very important to note from Matz's observations that some patients with these very high values for the non-protein nitrogenous constituents in their blood recovered completely. He attributes the changes to "protein injury, disintegration and autolysis accompanying excessive lung inflammation." The kidney, as previously stated, played no rôle. Phosphorus and chloroform poisoning are also accompanied by increased protein disintegration (Marshall and Rowntree). Other causes of destruction of body tissue might be mentioned, but it is believed that the examples cited are sufficient to show that an acceleration of the process of protein destruction is a common occurrence, that it usually indicates the presence of a serious condition, and finally that recovery may follow, even though it be present. The same conclusions are probably correct in regard to the protein destruction that at times is found in Bright's disease. The actual number of cases of nephritis in which protein disintegration has been observed are exceedingly few. It has already been mentioned that this process could not be demonstrated by the calorimeter. It may be of interest to mention the results obtained in conditions more closely related to Bright's disease than those detailed previously in this paragraph. In experimental uranium nephritis, an increased protein destruction is often present (Austin and Eisenbrey, Mosenthal(*a*), 1914). These results, like most of those in experimental nephritis, may be interpreted in one of two ways: either the symptom in question is the result of the induced nephritis, or both the nephritis and the accelerated protein catabolism are brought on by the same causative agent. It is much more likely that the latter supposition is the correct one. Under the circumstances, it is not justifiable to accept these findings as more than remotely suggestive; the situation would have an entirely different aspect if the poison or poisons responsible for the production of nephritis were known and experiments could be performed with them. Becker showed that in nephrectomized dogs, the heaping up of non-protein nitrogen in the blood is more rapid than would be caused by retention alone; he believes that the reason for this is an abnormally increased protein catabolism. If Becker's conclusion, that marked renal insufficiency may cause a disintegration of body

tissue is correct, a very important fact will have been developed. The report of Heilner, that urea ingestion may be responsible for protein destruction because there is a marked increase in urea excretion, is very far-reaching if true, but obviously needs extensive verification. Bradford's findings that in dogs with partially extirpated kidneys, 25 per cent of the original renal tissue remaining, there are polyuria, excessive urea output, rapid loss of weight and strength, finally terminating in death at the end of one to three weeks, are extremely suggestive of what may occur when marked renal insufficiency exists. These results and those of Becker supplement each other beautifully. It is obvious that the animal experiments must be repeated and the observations applied to patients before they can be accepted as proved and their importance fully realized. However, they suggest very significant possibilities.

In regard to studies in human nephritis, it has already been mentioned that calorimetric determinations failed to reveal the presence of an abnormal degree of protein destruction, and the unsatisfactory case reports of Von Noorden and Richter have been referred to. Frothingham and Smilie examined some patients concerning which they say: "A marked increase of non-protein nitrogen in the blood of over 150 mg. per 100 c.c. appeared from our cases to come on just a few days preceding death and we looked on it as a terminal phase of the disease." Mosenthal and Lewis reported several instances of protein disintegration in Bright's disease. All of these patients did not succumb; all of them, however, were seriously ill.

TABLE 18

DATA FROM A CASE OF (CONVULSIVE) NEPHRITIC TOXICOSIS IN A PATIENT SUFFERING WITH AN ACUTE EXACERBATION OF A CHRONIC NEPHRITIS, ILLUSTRATING THE OCCURRENCE OF PROTEIN DESTRUCTION

Date	Days Elapsed	Blood Mg. per 100 c.c.		Per Cent Urea N. of N.P.N.	Calculated Gm. N.P.N. Retained per Day	N. Gm.* Excreted Urine per Day
		N.P.N.	Urea N.			
April 1....		35	28	80		
6....	5	76	65	86	6	7 +
16....	10	151	124	82	6	7 +
21....	5	249	225	90	15	+
24....	3	426	351	82	45	+

* The patient could not be controlled and some of the urine was unavoidably lost. Anuria was not present at any time.

A case which illustrates the course of the process of protein destruction in Bright's disease is detailed in Table 18. In this patient the amount of nitrogen retained in grams was arrived at in the same way as described in the section on the nitrogen balance in nephritis. This man, a negro 46 years old, took very little food. The retention of 6 grams of nitrogen per day during the first 16 days, while more than 7 grams per day were eliminated in the urine would indicate some increase in the rate of protein

destruction. (During starvation, or on a low diet, about 8 grams of nitrogen a day may be considered as the normal amount that should be excreted by kidneys and intestines.) The retention of 15 grams per day during the next three days and of 45 grams per day for the last three days of life may be considered as absolute proof of the fact that a marked protein disintegration was taking place. In another section (creatin in nephritis) the evidence is cited that an increase of creatin in the blood towards the end of life in many nephritics bears witness to the fact that at this stage of their disease protein destruction often occurs.

It is probable that the same toxic substance that is responsible for the nephritis is also the cause for the loss of body substance, and that the nephritis is not the etiological factor upon which the increase in protein catabolism depends. In other cases, as suggested by the experimental evidence cited above, a marked renal insufficiency or an anuria may be found to be the cause for an increased protein disintegration. An accelerated protein destruction in nephritis is evidently to be regarded as a symptom of the disease. It usually marks a terminal state, though not in every instance; whenever it occurs, however, the patient's condition is grave. An abnormal degree of protein destruction in nephritis does not occur frequently and when present usually lasts only for a short period.

Fat Metabolism in Nephritis

The Utilization of Fat in Nephritis.—In nephritis the respiratory quotients obtained (Aub and Du Bois, Peabody, Meyer and Du Bois) indicate that fats are metabolized in a normal manner. The acidosis characteristic of certain stages of nephritis is not to be attributed to a faulty fat metabolism, as it is in diabetes mellitus, but is brought on by a deficient excretion of acids ordinarily eliminated by the kidney.

Lipuria (Chyluria) in Nephritis.—The occurrence of fat in the urine (except for the traces occurring in all urines) has been found rarely under any circumstances, unless the lymph channels were locked by parasites. Sanes and Kahn note that chyluria may occur, in the absence of parasites, by the passage of fat from the blood directly through the kidney epithelium; this is probably the result of a functional disturbance of the kidney cells. In their patient the fat in the urine rose as high as 6 per cent; the urinary fat in this instance was raised by a fat-rich diet and diminished by food low in fats. No signs of renal disease were noted in this case by Sales and Kahn, nor did they come to the conclusion, from a review of the literature, that chyluria was in any way characteristic of nephritis. Bauman and Hausmann report similar findings in a case of nephritis possibly of syphilitic origin. In their patient the lipuria was influenced by the amount of fat in the diet, there was no increase in the

blood cholesterol, the fat in the urine was as high as 0.168 gm. in four hours and, as in the first instance quoted, the increase in urinary fat was ascribed to altered permeability of the renal epithelium.

The Blood Lipoids in Nephritis.—The analyses of blood lipoids have been carried out with great enthusiasm during the past few years. The results have not been uniform. This is in part due to the fact that the chemical methods have not been thoroughly standardized, and in part, because the same types of nephritis apparently do not exhibit constant variations from the normal throughout their course. However, some very striking observations have been made and they promise to be of considerable importance when they will be more thoroughly understood.

TABLE 19

BLOOD LIPOIDS, PER CENT, IN NEPHRITIS ACCORDING TO BLOOR(*d*). (1917)

	Normal	23 Cases of Nephritis	
		Highest Value	Lowest Value
Total Fatty Acids:			
Whole Blood	0.36	0.64	0.38
Plasma	0.39	0.67	0.30
Corpuscles	0.32	0.86	0.30
Lecithin:			
Whole Blood	0.30	0.40	0.14
Plasma	0.20	0.27	0.14
Corpuscles	0.42	0.74	0.29
Cholesterol:			
Whole Blood	0.22	0.28	0.15
Plasma	0.23	0.24	0.14
Corpuscles	0.20	0.30	0.16
Fat:			
Plasma	0.13	0.46	0.12
Corpuscles	0.04	0.37	0.00

A summary of some of Bloor's analyses is given in Table 19. These figures cover the field fairly well and indicate what may be encountered in many instances. Bloor(*d*), from these determinations and a review of the reports up to 1917, comes to the following conclusion: "The abnormalities in the blood lipoids in severe nephritis were found to be high fat in plasma and corpuscles and high lecithin in the corpuscles. The cholesterol values were practically normal. These abnormalities are the same as are found in alimentary lipuria and for this reason are regarded as the result of a retarded assimilation of fat in the blood, which in turn is thought to be one manifestation of a general metabolic disturbance brought about by a lowered 'alkali reserve' of the blood and tissues." Bloor notes that in most of his cases an acidosis was probably present and it may be accepted that a decreased blood and tissue alkalinity plays a part in producing these slight changes in the blood lipoids demonstrated by Bloor. It must be recognized, however, that there may be other causes as well which will increase the blood lipoids in nephritis. These will be discussed subsequently.

A milky plasma—lipemia—has been frequently observed in nephritis. (Fisher, B.; Chauffard, La Roche and Grigaut; Widal, Weill and Laudat; J. Müller(*c*).) Greenwald (1915) noted a high lipoid phosphorus in the blood of nephritics; Erben found increased values for lecithin and fat in a sub-chronic case. J. Müller and Bonniger demonstrated an increase in the total blood lipoids.

The greatest amount of attention has been devoted to the cholesterol content of the blood. This may be within normal limits in all cases of nephritis (Bloor(*d*), Denis(*c*), Kahn(*c*)) or may be found to be increased moderately in every form of nephritis (Gorham and Myers) or may be normal in certain types of Bright's disease while it is distinctly increased in others (Stepp(*b*), Kollert and Finger, Epstein(*b*), Port(*b*)). It is gradually becoming apparent that the findings of the last group of authors are the correct one, namely, that the most marked hypercholesterinemia is present in parenchymatous nephritis or nephrosis (a form of kidney disease characterized by edema, albuminuria and usually a low blood pressure). It is not present in every case, nor does it necessarily remain high when it has increased. These facts may account for the variety of results that have been obtained thus far. The following data are those of Epstein. (Table 20.)

TABLE 20

CHOLESTERIN CONTENT OF BLOOD SERUM IN NEPHRITIS. (Epstein)

Diagnosis	No. of Cases	Cholesterin Content Blood Serum Milligrams per 100 c.c.		
		Average	High	Low
Chronic interstitial nephritis	24	174	265	100
Uremia	5	133	194	87
Arteriosclerosis	7	163	218	100
Cardiac disease	19	157	294	104
Bichlorid of mercury poisoning	2	127	130	125
Chronic parenchymatous nephritis	9	559	1230	333

The cause of the increased blood cholesterol in nephrosis is not clear. It is not due to insufficient renal activity, for the lipoids, except for traces, are not present in the normal urine. That it is due to some metabolic disturbance is stating an obvious fact and does not further the solution of the problem. It has been attributed to non-utilization of ingested or mobilized fat inasmuch as the lipemia disappeared on a low fat diet (Epstein and Rothschild). Denis makes a similar explanation to account for the low values found in some cases suggesting that they are due to a diet which contains little cholesterol. Port(*b*) believes that the cholesterol may originate from degenerating epithelial cells or to a disturbed action of the suprarenal gland. Whether in nephritis the suprarenal gland plays an active rôle in producing cholesterin (Albrecht and Weltmann) or

whether it becomes secondarily infiltrated (Landau), appears to be purely a matter of speculation at the present moment. All the theories concerning the blood lipoids in nephritis appear to be in much the same plight.

There apparently is no definite relation between the degree of cholesterinemia and the blood pressure or the non-protein nitrogen of the blood (Denis(*c*), Gorham and Myers, Schmidt, Henes). In the uremic state the blood cholesterol may be normal (Stepp(*b*)) or diminished, even if there has been a previous hypercholesterinemia (Henes).

Carbohydrate Metabolism in Nephritis

Utilization of Carbohydrates in Nephritis.—The utilization of carbohydrates, both quantitatively and qualitatively, as shown by calorimetric determinations, is normal in nephritis (Peabody, Meyer and Du Bois, Aub and Du Bois). It is important for the therapeutist to realize this inasmuch as the digestion of carbohydrates constitutes the best means to lower the level of protein metabolism and thus diminish the amount of work demanded from the kidney.

The relation of carbohydrates to acidosis in nephritis is different from that in some other forms of acidosis. Diabetic acidosis, the best known type of this condition, is the result of the retention within the body of incompletely oxidized fatty acids, whose final change to carbon dioxid and water depends upon the simultaneous utilization starches. In nephritis, glucose is metabolized along normal channels and another cause must be sought for the acidosis. This is found in the retention of acid substances by an insufficient kidney.

In the succeeding chapter, the subject of blood sugar in nephritis is discussed; it becomes very evident from the facts therein that, in some cases at least, the blood sugar is higher than normal and that there must be some interference with the intermediary metabolism of the starches. The possible reasons for this will be taken up subsequently. These findings are not necessarily at variance with those of Du Bois and his coworkers previously quoted. It may be that the particular patients investigated with the calorimeter did not have a high percentage of glucose in the blood, or that the rise in blood sugar is brought about by a series of changes which are not reflected in such determinations.

The Blood Sugar in Nephritis.—Since Neubauer (1910) demonstrated an increased blood sugar in nephritis, there have been many investigations of this subject. The results have varied a great deal. Taking all the reports into consideration (Bing and Jakobsen, Frank(*b*), Hagelberg, Hamman and Hirschman, Hopkins, Janney and Isaacson(*c*), Myers and Bailey, 1916), E. Neubauer (1910), O'Hare(*c*)(1920), Port(*a*), Rolly

and Oppermann, Stilling, Tachau, Weiland(*b*), Williams and Humphreys) it is very evident that the blood sugar in nephritis is increased in some cases and not in others; this variability of the blood sugar occurs apparently whether the nephritis is acute or chronic, whether it is of the "parenchymatous" or "interstitial" type, whether or not it is accompanied by hypertension, uremia, apoplexy or an increased blood urea; furthermore, the following conditions, which may be considered as having some relation to nephritis, show the same inconstancy in the blood sugar level, eclampsia, essential hypertension, and arteriosclerosis. Williams and Humphreys found the blood sugar in nephritis to be as high as 0.25 per cent, Myers and Killian(*a*)(1917) 0.32 per cent and Mason 0.22 per cent in acute nephritis.

Some of the authors mentioned above have investigated this matter further and have determined the changes occurring in the blood sugar after the administration of given amounts of glucose. These "blood sugar curves" were frequently prolonged and rose to levels above the normal; however, some individuals with normal reactions were found. The sugar in the blood in nephritis may therefore be regarded as having, in some cases at least, the characteristics found in diabetes mellitus.

A very puzzling feature about this abnormality is the fact that apparently it bears no constant relation to the severity of the renal involvement or to any one of the common complications of nephritis. It is worthy of note that as the investigations concerning blood sugar progress, there are a constantly increasing number of conditions in which it is found to rise above the normal. The well known facts, that it is associated with, an increased activity of the thyroid, suprarenal and hypophyseal glands, experimental deficiency of the pancreas, and diabetes mellitus may be cited; furthermore, recently similar blood sugar curves have been found in some cases of syphilis (Rohdenburg, Bernhard and Krehbiel) and in gastro-intestinal cancer (Friedenwald and Grove). The occurrence of blood sugar reactions, resembling those of diabetes mellitus, in so many apparently widely different diseases, and the inconstancy of its presence in nephritis or any of its more usual complications, make it very difficult to assign a definite cause for it.

An explanation of these blood sugar abnormalities has frequently and somewhat thoughtlessly been attributed to a retention of glucose by the kidney because of a raised renal threshold to this substance. Such a mode of reasoning is obviously wrong, as the kidney ordinarily does not excrete an appreciable amount of sugar and thus can not be responsible for its increase in the blood; the cause for this phenomenon must be sought in some metabolic disturbance which mobilizes the blood glucose with abnormal rapidity.

Various other interpretations have been given. E. Neubauer (1910), in the original communication on this topic, suggested that it was due

to the presence of an increased amount of epinephrin. This theory, as do all those that postulate a hypersecretion of the suprarenal glands, awaits confirmation. Pierce and Keith offered some experimental evidence that ordinarily sugar did not appear in the urine because the kidney utilizes sugar as presented to it. While these authors did not attempt to explain the high blood glucose of nephritis in this way, their work is suggestive of the possibility that a damaged kidney will not consume the usual amount of sugar and that, consequently, it may accumulate in the blood.

The most valuable explanation thus far offered is that of Myers and Killian(*a*)(1917). They showed that many cases of nephritis have an abnormally high figure for diastatic activity of the blood; the patients with an increased blood diastase are the ones that have a high blood sugar. Renal insufficiency is supposed to be responsible for the high blood diastase. The latter mobilizes glucose from the liver and muscle glycogen, thus making the series of events complete. Previously an increase of diastase in the body and diminution of liver glycogen had been demonstrated in various forms of renal injury (Grünwald, Orkin). Recently Lewis and Mason expressed the view that the diastase of the blood in nephritis showed no direct relation to the type of renal lesion, to the degree of kidney involvement or the progress of the disease. This observation does not necessarily impair the soundness of Myers and Killian's theories. O'Hare(*c*)(*d*)(1920) has suggested that sclerosis of the arteries of the pancreas diminishes the functional efficiency of that organ and that certain cases of hypertension may therefore be regarded as potential cases of diabetes mellitus. This undoubtedly is true in some instances of essential hypertension and nephritis; however, it is certain that this explanation will not suffice to account for all the cases of hyperglycemia occurring in nephritis. The problem of the cause of the rise of blood sugar in nephritis awaits a final solution.

The renal threshold to the glucose of the blood presents some very interesting facts. The normal threshold is at a level of about 0.17 per cent (Hamman and Hirschman). It may be considerably raised in acute or chronic nephritis (Mason, Neubauer (1910)). Neubauer had one case in which the blood glucose rose to 0.36 per cent without glycosuria. In this connection, as with many of the other phases of nephritis, there are discrepancies that make it certain that other conditions can interfere with renal function and that lesions of the kidney do not involve the whole organ in uniform fashion. Thus, in some cases of diabetes mellitus in which the kidneys gave no evidences of nephritis, the blood sugar was as high as 0.32 per cent, while the urine remained sugar free, and in one patient, suffering with nephritis and a considerable impairment of renal function, the glucose threshold was less than 0.10 per cent (Mosenthal and Lewis(*b*), 1917).

Mineral Metabolism in Nephritis

The Chlorids of the Blood in Nephritis.—The observations on the chlorid content of the blood have thus far defied satisfactory interpretation. This is due in part to the fact that insufficient attention has been paid to the medium—whole blood, plasma or serum—in which the chlorid content was determined. The normal sodium chlorid concentration in whole blood is 4.5 to 5.0 grams per liter, while that in the plasma is 1.2 grams higher. If the blood is allowed to stand the salt in the plasma increases due to a loss of carbon dioxid from the plasma, and a consequent shift of sodium chlorid from the corpuscles to the plasma. On this account it would appear that chlorid determinations on the plasma cannot be regarded as very accurate and that many of the observations will have to be repeated with whole blood (for full discussion see section on normal tissues).

McLean(*a*) found the lowest plasma chlorid in his series in a diabetic patient: 5.0 grams per liter, and the highest, 8.4 grams, in a cardionephritic case just before death. Host showed how the chlorids in the blood may drop in acute nephritis as the edema diminishes and the kidneys eliminate increased amounts of water and sodium chlorid. The blood chlorids in his cases while edema existed were respectively 5.8, 5.5, 5.1, 5.2 grams per liter; after the subsidence of the edema the values dropped to 4.5, 4.7, 4.6, and 4.5 gm. Austin and Jonas have confirmed the occurrence of such low figures. They found the plasma chlorids as low as 4.6 gm. per liter in one case of advanced glomerulonephritis 5 days before death. Atchley's observations in acute nephritis bear out Host's results.

However, Atchley had one case which was rather confusing in the light of the above findings. The results in this patient go far to show that the blood chlorids are not controlled by one factor but by many. In one of his observations the plasma chlorids dropped from 6.19 to 4.45 grams per liter during a period of practical suppression of urinary chlorid excretion; Atchley offers two possible explanations of this phenomenon: first, that the chlorids may have been forced into the corpuscles by a change in the carbonate concentrations, the Zunst reaction; second, that an increase in the other blood constituents such as urea may demand an adjustment to preserve the osmotic balance. Atchley believes his case to be most important as illustrating that there may be a very great change in the plasma chlorid concentration independent of intake or urinary excretion and paradoxical to the apparent chlorid balance.

Diet will certainly modify the blood chlorids to a certain extent. The crudest and most telling way to effect this is to give a considerable quantity of sodium chlorid by mouth. After the ingestion of 10 grams the author has found a distinct rise of chlorids in the whole blood. Austin and Jonas

produced an increase of 1 gram per liter in the plasma within one and one half hours after the administration of large amounts of salt to dogs by stomach tube. The chlorid content of the plasma returned to its previous level in 24 to 48 hours. Restriction of sodium chlorid in the food of nephritic patients will often reduce an excessive degree of blood chlorids. Thus Myers cites one instance of advanced nephritis in which the sodium chlorid of the whole blood dropped from 5.94 grams to 3.94 grams per liter through suitable dietary restrictions. In normal dogs Austin and Jonas could produce no drop in the plasma chlorid level either by a diet low in salt or by free flushing of the body with water. They come to a very interesting conclusion in regard to this matter: "These experiments indicate, therefore, that in those cases of clinical nephritis in which, following the use of a low chlorid diet, the plasma chlorids fall distinctly below normal, this depression of the plasma chlorids is evidence of disease and not merely a consequence of the patient's régime."

There are two possible factors that may be of influence in raising the blood chlorids that should be kept in mind from the clinical point of view. First, it is perfectly evident to any one who has listed a series of blood chlorid determinations and compared them to the level of other renal excretory products in the blood, that when renal insufficiency exists, the blood chlorids often rise; this synchronous occurrence of renal insufficiency and rise in blood chlorids is, however, far from constant. This is not surprising as the kidney may be unable to excrete one substance while it retains another, or the effect of diet may make itself felt. It is only natural to suppose that a poorly functionating kidney will bring about a retention of chlorids, but it must be realized that this explanation does not account for all the variations that apparently occur in the blood chlorids. Second, there is an evident attempt of the body to keep its fluids in osmotic balance; this has already been alluded to in a theory put forth by Atchley when he supposed that the chlorids in the plasma may diminish as the blood urea rises; on this basis the low blood chlorids found in diabetes may be assumed to be caused by the hyperglycemia present in that condition. Another finding which substantiates this idea is the very bizarre and marked fluctuations obtained in the chlorid concentrations in the blood after the administration of 100 grams of glucose. W. W. Herrick has shown the author some very interesting examples of such observations. The above theories undoubtedly offer an explanation of some of the variations occurring in the blood chlorid concentration; they do not account for them in full and many further observations will be necessary before the problem of what influences control the chlorids in the blood in nephritis will have been cleared up.

The subject of chlorids in nephritis is discussed from another point of view under the heading of the Chlorid Threshold in Nephritis, in the section on Renal Function.

Phosphates and Calcium of the Blood in Nephritis

According to Greenwald there are three classes of phosphorus compounds in the blood serum: lipoid, inorganic and protein. Of these the protein constitutes a very small fraction. The normal figures are given in Table 21. In nephritis as a rule, when the excretion of phosphates is inadequate, inorganic phosphorus accumulates in the blood, the lipoid fraction rarely rises and the protein phosphorus apparently never increases. Usually, as the non-protein nitrogen increases the inorganic phosphates do as well. That is, a renal insufficiency causing retention of the one also brings about the retention of the other. In some cases these do not run parallel, indicating that there is a different process within the kidney responsible for the elimination of each. All these facts are brought out in Table 21 taken from Greenwald's researches.

TABLE 21

PHOSPHORUS OF THE BLOOD IN NEPHRITIS. THE INCREASE OF PHOSPHORUS IS USUALLY IN THE INORGANIC PHOSPHATES, THOUGH THE LIPOID PHOSPHATES MAY ALSO BE INCREASED. THE INCREASED BLOOD PHOSPHATES ARE GENERALLY, BUT NOT ALWAYS ACCOMPANIED BY AN INCREASE IN THE NON-PROTEIN NITROGEN OF THE BLOOD. (Greenwald)

	Mg. per 100 c.c. Blood			
	Non-protein Nitrogen	Phosphorus		
		Inorganic	Lipoid	Protein
Normal	30-40	2.0-6.8	6.6-13.0	0.5
Nephritis	19.3	3.3	9.7	1.8
"	31.4	20.2	12.9	0.1
"	111.0	6.8	10.2	0.1
"	255.0	12.7	8.2	0.0
"	200.0	12.5	7.8	0.4
"	103.0	21.1	16.7	0.0
"	42.8	12.3	36.2	0.9

There is a tendency for the plasma phosphates to accumulate very rapidly towards the end of life. A high phosphate volume in the plasma indicates a poor prognosis, a low phosphate that there is no immediate danger. (Denis and Minot(*b*)) (see Table 22.)

The increase of phosphates in the blood is due to renal insufficiency, and the resulting accumulation of urinary constituents in the body. About 90 per cent of the phosphates in the urine is in the form of acid phosphate. A retention of this material would consequently be responsible for acidosis. This Marriott and Howland believe, would account for the acidosis in nephritis, although they are unprepared to say that it is the sole factor. Associated with the retention of phosphates is a marked reduction of

TABLE 22

DATA OF A CASE OF CHRONIC NEPHRITIS WITH UREMIA AND A FATAL TERMINATION, SHOWING HOW RAPIDLY THE INORGANIC PHOSPHATES MAY ACCUMULATE IN THE BLOOD TOWARDS THE END OF LIFE IN NEPHRITIS. (Denis and Minot(*b*)).

Date	Mg. per 100 c.c. Plasma	
	Non-protein Nitrogen	Inorganic Phosphorus
March 10	2.8	105
" 15	9.4	167
" 19	15.0	200

calcium in the serum. This is due to the fact that when the phosphates no longer pass out in the urine a compensatory elimination through the intestines occurs. The phosphates are excreted in this way only when combined with calcium. The calcium of the blood in such cases of nephritis is necessarily diminished. Conversely, the administration of calcium leads to an increased elimination of phosphates by the bowels. The following table illustrates these facts.

TABLE 23

THE LOW CALCIUM CONTENT OF THE BLOOD, AND THE LABORATORY EVIDENCES OF ACIDOSIS ACCOMPANYING AN INCREASE IN THE INORGANIC PHOSPHATES OF THE BLOOD IN NEPHRITIS ARE SHOWN. (Marriott and Howland)

		Mg. per 100 c.c. Blood		Alveolar CO_2	Plasma CO_2	Diagnosis
		P	Ca			
Normal		1-3.5	10-11	40-45	60-65	
Cases with Acidosis	1...	22	4	21	....	Chronic nephritis, uremia, fatal
	2...	11.3	9	25	....	Congenital polycystic kidney
	3...	19	5.3	10.7	....	Double pyonephrosis, uremia, fatal
	4...	10.3	7.2	....	40	Chronic nephritis, fatal
	5...	13	1.5	....	11	Chronic nephritis, uremia, fatal
	9...	18	3	6.4	....	Polycystic kidney, uremia, fatal
Cases without Acidosis	1...	5	8.3	....	....	Chronic nephritis
	2...	5	10	....	61.4	Chronic nephritis, fatal
	3...	4	8	....	86	Chronic nephritis, fatal

Renal Function

The kidneys eliminate certain substances presented to them by the blood; the only additional work they perform is the synthesis of hippuric acid. Even when the kidneys are physiologically and anatomically intact there may be a deficiency in urinary excretion. Thus, oliguria or anuria

may occur if the blood becomes very inspissated, as in cholera; cardiac decompensation results in retention of water and chlorids; a dilute blood, as in the anemias, brings about a low urinary concentration; cystitis and pyelitis may do the same; obstruction of the ureters, or urethra by stone, carcinoma, hypertrophied prostate or stricture at times cause marked renal insufficiency, etc. It is obvious, from what has been briefly noted, that the term renal function, in the clinical sense, is not synonymous with kidney efficiency, but includes all the processes in the body that influence the kind and amount of urine that passes the urethra. The physician, dealing with Bright's disease, must necessarily bear this definition, and its significance, in mind when interpreting tests for renal function.

Tests for renal function may be considered as falling into three groups:

1. Tests for renal function "as a whole."

2. Tests that attempt to determine the anatomical location of the impairment of efficiency, tubules, glomeruli, or blood vessels.

3. Tests whose purpose it is to ascertain the power of the kidneys to eliminate one or more of the substances—such as urea, sodium chlorid, creatinin, uric acid, water, etc., which are ordinarily excreted in the urine.

Such a classification of tests for renal function is very useful. It furnishes a synopsis of the development of this branch of medical science and in addition serves to point out the deficiencies in the present day knowledge of the action of the kidneys under physiological and pathological conditions. The earliest successes in obtaining an idea of renal efficiency was by tests which indicated the ability of the kidney to functionate "as a whole." This phrase was advocated by the observers who favored these procedures. It is very expressive inasmuch as the substances used—principally dyestuffs—do not parallel any of the known excretory substances in the urine absolutely, and are not, as far as generally acknowledged, eliminated by a definite portion of the renal structure. The phenolsulphonephthalein test is the one most widely used, and is the only one of this group which will be considered in detail; it has been of great service in promoting the knowledge of nephritis and is still of supreme importance to the physician with limited laboratory facilities; it has, however, been largely replaced by procedures that give information regarding the specific functions of the kidney. It has gradually come to be appreciated that such specific tests give the greatest amount of information and that renal efficiency is hardly ever curtailed as a whole, but to a greater extent in certain directions than in others. To be oriented on these points tends to a more accurate functional diagnosis and better therapy.

The Phthalein Test.—"Phenolsulphonephthalein, which was first described by Remsen, is a bright red crystalline powder, somewhat soluble in water and alcohol and readily soluble in the presence of alkalies. The drug, as determined by Abel and Rowntree, is non-toxic, non-irritant

locally, and is excreted practically entirely by the kidneys and with extraordinary rapidity, appearing in the urine normally within a few minutes of injection. In alkaline solution it presents a brilliant red color which is ideally adapted for quantitative colorimetric estimation." (Rowntree and Geraghty.)

Technic.—About one-half hour before the drug is injected 400 c.c. of water are given. One c.c. of a specially prepared solution containing 6 mg. of phenolsulphonephthalein are injected intramuscularly, preferably in the lumbar muscles. At the end of two hours and ten minutes (ten minutes to allow for absorption and two hours for excretion) the urine is collected. It is made decidedly alkaline with a sodium hydroxid solution (10 to 25 per cent) diluted to one liter and the percentage of phthalein excreted is determined by comparison with the standard in a suitable colorimeter. There are many variations from this technic (Rowntree and Geraghty) which may be employed according to various indications or opinions.

In the author's experience subcutaneous injections have been extremely unsatisfactory and intravenous injections have occasionally produced undesirable reactions. Keith and Thomson noted reappearance of hematuria in acute nephritis following the injection of phthalein. Such untoward experiences are rare and should not act as a deterrent to an employment of the test. In pregnancy the phthalein injection is not followed by an excretion as in other individuals; under these circumstances, therefore, it is of no value. Kendall finds that the tissues have the power to destroy phthalein; this may interfere with the test theoretically and may account for occasional bizarre findings, but certainly does not serve to annul the worth of a most useful procedure.

Some inaccuracies that occur may be due to the fact that the solution of the dye for injection is not of the proper strength, either because it has been carelessly compounded or because it has deteriorated. If precautions are taken to have the standard and injected material of the same proportionate value many of the apparent discrepancies will be obviated.

The normal excretion of phthalein is 60 per cent or more in two hours (Rowntree and Fitz) though in many instances the lower normal limit appears to be 50 per cent. In children the usual output is somewhat higher, 76 to 81 per cent (Tileston and Comfort(*b*); Hill).

Clinical Significance.—The first question to be dealt with under this heading is, What does a diminished excretion of phthalein signify? To answer that it indicates a subnormal renal function is not entirely satisfactory to-day. In addition, the problem of which anatomical portion of the kidney—tubules, glomeruli or blood vessels—is involved, or of which excretory product—water, salt, urea, etc.—parallels phthalein elimination has to be met. "Experimental evidence seems to indicate that phenolsulphonephthalein is excreted mostly by the tubules, but also to a slight

extent by the glomeruli" (Rowntree and Geraghty). This statement may satisfy our craving for knowledge in certain directions. It is doubtful whether any information regarding the excretion of substances by the tubules or glomeruli at the present moment is of more than theoretical interest to the clinician, because of the very undeveloped state of the physiology and pathology of these structures. Therefore, this aspect of the problem needs no further discussion.

The other portion of the original question as to what renal excretory products phthalein parallels is of much greater significance. With the development of chemical methods a greater demand has been made of renal functional tests than previously; these methods tell specifically what substances are retained and furnish clear-cut indications in regard to therapy and prognosis. Many attempts have been made to associate phthalein elimination with one or the other of the renal excretory products. The experimental work of Marshall and Kolls possibly comes nearest to a solution of this question. They find that the excretion of sodium chlorid, water and urea, do not follow the phthalein while creatinin does; furthermore, the very interesting and valuable observation is made that the relative amounts of water and chlorids eliminated depend more upon the blood flow than upon the amount of kidney tissue present, while the importance of the influence of these factors is reversed in the case of creatinin and phthalein.

From the clinical point of view, it is well established that the retention of creatinin in the blood occurs only when the elimination of phthalein is very much below the normal. The compensatory factors for the excretion of creatinin appear to be very great. Therefore, an inference regarding the retention of creatinin can not be made because the phenolsulphonephthalein test shows an impairment of renal function. The possibility that the phthalein test parallels the total amount of actively functionating kidney substance, irrespective of the volume of blood flow or nervous influence, lends a significance to this test which makes it of much greater clinical importance than formerly.

For many physicians the phthalein procedure must of necessity remain the method of choice for testing renal function. It requires only a very limited equipment for its performance and no profound knowledge for its interpretation. As medical science develops it will undoubtedly be replaced by tests which demonstrate the ability to excrete certain substances that have a direct bearing upon the shaping of treatment. Theodore Janeway(*b*), in 1913, made a statement, as true to-day as it was at that time, which gives us the status of the phthalein test as it promises to be regarded almost indefinitely: "The test brought out by Dr. Rowntree is a test which aims at the solution of the old pressing clinical problem, the prognosis, especially as a guide to a surgical procedure. It is admirable and answers that need better than anything else that we possess to-day. From the

medical standpoint the test is a rough quantitative measure of the total kidney function—whatever that may be; I do not think that we are in a position at the present time to say what is the total kidney function."

Clinical Value.—The worth of the phthalein test has been established by too numerous observations for individual mention. The normal excretion of the drug in two hours after the intramuscular injection is 60 per cent; diminishing values to zero may be found; life is compatible with no elimination of phthalein whatsoever, though the outlook is always serious under the circumstances (the author has noted one case in which life was maintained for a period of two and one-half years though repeated tests during that time showed that no phthalein or only traces would be present in the urine). Usually any figure of twenty per cent or less may be regarded to be of serious omen.

In certain conditions in which the kidney may be considered as being "irritated" or overactive, there is a distinct elimination of phthalein above the normal. Lewis has shown how this phenomenon occurs in early chronic diffuse nephritis, fever, hyperthyroidism, and in some cases of hypertension. Such "supernormal" phthalein figures are accompanied by similar findings in the urea excretion. These facts will be discussed in detail under the heading of the coefficienct of urea excretion.

In nearly all forms of nephritis apparently the idea of Marshall and Kolls that the amount of phthalein eliminated depends upon the amount of actively functionating kidney substance seems to hold true. There is one form of nephritis, the so-called parenchymatous (characterized by albuminuria, diminished salt excretion and edema), in which the phthalein may be put out not only in normal amounts but even in still larger quantities. Thus Pepper and Austin(*a*) report one such case in which as much as 82 per cent was found in two hours, and Baetjer, four cases with outputs varying from 69 to 90 per cent. These findings and those mentioned in the preceding paragraph are reminders of the fact that nephritis is a disease whose severity in some instances can not be measured by renal function alone.

Tests for Function of the Glomeruli and Tubules

The idea of correlating clinical signs, symptoms and tests with pathological changes in the kidney has been an alluring goal for a long time. Many researches have shown the futility of solving this problem satisfactorily. It is doubtful whether this can ever be accomplished because any renal functional test reflects not only the state of the kidney, but that of the whole body. Cardiac influences, disturbances of the nervous system, abnormal water metabolism, pathological conditions of the ureter and bladder, etc., give pictures of abnormal renal function which can not be distinguished from those whose cause resides solely in the kidney.

Another element that militates against the linking of clinical observation with the site of the renal anatomical lesion, is the lack of an accurate knowledge of kidney physiology. This is a problem which still remains in the clutches of theory and is not a realization. Bowman believed that the glomeruli excreted water and the tubules the urinary solids; Ludwig's (*b*) idea was that all the urinary constituents originated in the glomeruli by filtration and that concentration was brought about by absorption of water in the tubules; Cushny's(*b*) "modern theory" is somewhat similar: first, there is a purely physical filtration through the glomeruli of all the constituents of the plasma except the colloids, and, secondly, there is a resorption by the vital activity of the tubules, which modifies the filtrate so that it forms the urine ultimately excreted. Even a superficial acquaintance with the histology of the kidney would indicate that the water of the urine must originate in the glomeruli; the question of how the solids pass out of the kidney is another matter. The conception of reabsorption of water by the tubules is ingenious but has to be regarded as purely theoretical. Recently, Oliver has conclusively shown that there is an active secretion of urea by the proximal convoluted tubules and that this secretion is added to the urea which passes through the glomerular filter with the other crystalloids of the blood plasma. This observation confirms the findings of various workers that dyes, uranium, phosphates, urea, uric acid and salt may be excreted by the tubules. This fact is important because it indicates that the tubules play a very active rôle in the excretion of the body's waste products and not a negligible one, as they would if their sole function were to absorb water from the glomerular filtrate.

Even conceding that a fairly satisfactory theory of renal physiology has been developed, it becomes very difficult to apply this to the interpretation of clinical tests. The following examples may make this statement a little clearer: should the glomeruli cease to function because they are inflamed, congested, or because of lack of fluid supply, etc., the tubular activity must necessarily be suspended since there is no water to carry away the products which they eliminate; should the tubules become obliterated by pressure in the interstitial spaces as in congestion, or blocked by the accumulation of débris resulting from degenerative or inflammatory products within them, evidence of function of the corresponding glomeruli must necessarily be lacking for the material excreted by them can not pass on to the collecting tubules. A recent observation of Richards, that, in the frog at least, not all of the glomeruli are functionating all the time, but that they have quiescent periods, opens up many obvious possibilities that may inject new aspects into the perplexities of interpreting renal functional tests properly.

From what has been said in the last three paragraphs, it becomes evident that tests for renal function can not be regarded solely in the light of renal pathology, nor can they be valued as a sign of existing function

dominated entirely by the kidney, but that they are the expression of the body's power to eliminate urinary excretory products at the urethra; diseases of the hypophysis, pneumonia, excessive vomiting or diarrhea, fever, diabetes mellitus, renal calculus, urethral stricture, hypertrophied prostate, pyelitis, cystitis, myocardial insufficiency, paralysis of the bladder, polycystic kidney, etc., may all profoundly influence renal activity and mold the results of functional tests. It is obvious that in their interpretation clinical judgment and knowledge will always play a larger part than a set of rules which defines the limitations of tubular or glomerular activity or even of "renal function as a whole."

There has been only one thorough attempt made to associate the impaired function of anatomical structures (glomeruli and tubules) with the pathological physiology of the kidney in nephritis. This is that of Schlayer and his associates. Some of the extensive conclusions of these authors are of the greatest importance, while others have not proved to be of practical value; however, they are all of considerable interest and it is well worth while to take them up briefly, at least.

Schlayer's Theories of Renal Function in Nephritis

The living kidney was studied by various means and the results were given clinical application. The kidney was found to have two functional units, the blood vessels (glomeruli) and the tubules. The excretory substances resorted to as criteria for the efficiency of these structures were water, which is controlled by the glomerular activity, and salt, which is eliminated by the tubules. Inasmuch as these materials form part of the body's tissues, it is evident that extrarenal factors may influence the amounts present in the urine. Therefore, in addition, test materials were chosen which should not be affected by extrarenal influences. These were lactose which was found to represent the activity of the blood vessels, while potassium iodid was regarded as an excretory product of the tubules. The only extrarenal factor affecting the excretion of these substances is passive congestion which delays the elimination of lactose.

Various degrees of damage to the blood vessels result in the excretion of very changing quantities of urine. A slight impairment produces an irritability or hypersensitiveness of the blood vessels and brings about a polyuria; a further weakening of the vascular function causes the urine volume to diminish and resemble the normal quantity, the stage of "normaluria"; finally, marked impairment results in oliguria. Table 24 on page 356 illustrates this conception.

The underlying principle that a slight lesion may result in superfunction and only a severe impairment produces hypofunction, as measured by any of the conventional tests, holds true for the kidney and probably for the activities of many other organs. This phenomenon is al-

TABLE 24

SCHEME OF PROGRESSIVE IMPAIRMENT OF FUNCTION OF THE KIDNEY BLOOD VESSELS (GLOMERULI) AND THE INFLUENCE THIS HAS UPON THEIR ACTIVITY ACCORDING TO SCHLAYER. (ANY RENAL FUNCTION SUCH AS THE EXCRETION OF UREA, SALT, ETC., APPARENTLY PASSES THROUGH THE SAME PHASES, AS THE CORRESPONDING FUNCTION BECOMES PROGRESSIVELY INVOLVED)

Functional Impairment Blood Vessels	Reaction of Blood Vessels to Stimuli	Volume of Urine Excreted	Deficiency in Lactose Excretion
0	Normal	Normal	0
+	Hypersensitive	Polyuria	+
++	Pseudonormal	Pseudonormal	++
+++	Hyposensitive	Oliguria	+++
++++	No Reaction	Anuria	++++

luded to under the coefficient of urea excretion and the phthalein test. Such a conception has proved to be most valuable in explaining many of the very complex changes that occur in nephritis, and is by far the most important part of Schlayer's contribution to the study of renal function.

The excretion of the test substances, not found in the body tissues, lactose and potassium iodid, follows a somewhat different course. The elimination of these materials is progressively diminished and there is no period of supernormal urinary discharge as there is in the case of water (see table 24).

The theories of Schlayer and his associates have been severely criticised by a number of authors. These objections have recently been summarized by Volhard. Briefly they are that in the animal experiments the so-called impairment of vascular function is largely, if not entirely, due to a drop in blood pressure and not to changes in the renal vessels, that the experiments with the vascular nephritides depress function so quickly that any experimental observation is impossible and that the findings depend more on the rapidity of the effect any toxic substance has upon the kidney than upon the particular renal anatomical unit which may be involved. From the clinical point of view, Volhard is unable to correlate Schlayer's functional tests with the very evident anatomical lesions as they exist in some cases. Furthermore, the procedures for the lactose and potassium iodid tests are so cumbersome that their use is precluded as a routine measure in clinical medicine.

These criticisms may be correct even though any one who has worked with Schlayer's methods can find a plausible interpretation for the findings in every case. However, it must be admitted that, the actual demonstration of what rôle the glomeruli, tubules and blood vessels play in the production of urine, either in health or disease, has not been accomplished. Therefore, any theory of renal function in nephritis rests on an unsatisfactory physiological basis and can not have our full confidence. The fact that slight renal impairment leads to overfunction and marked involvement to curtailment of urinary activity has been proved by many tests with

numerous substances (urea, salt, water, phthalein) and may therefore be accepted as an empirical truth. It may arouse speculations as to the rôle the glomeruli and tubules play in this connection. This unsolved side of the problem, however, need in no way impair the clinical importance of the observation. From the clinical point of view the use of lactose and potassium iodid to determine renal function has been found to be impracticable not only because the methods are difficult to carry out, but also because the significance of the tests is not clear (Rowntree and Fitz, Volhard, Siebeck(*b*), Monakow(*a*) and others).

Technic of the Lactose and Potassium Iodid Tests. Lactose.—About 70 c.c. of a 10 per cent solution is put into an Erlenmeyer flask; a fresh flask is used for each test; the lactose solution is pasteurized on three successive days at 75° to 80° C. for four hours (heating to 100° C. gives the lactose a brown color and makes subsequent readings in the polariscope difficult or impossible). Unless the directions are carefully followed untoward reactions, such as a chill, may follow; 20 c.c. of this solution (i e. 2 grams of lactose) are injected intravenously; the urine is examined every hour or one-half hour subsequently by means of Nylander's reaction to determine the absence or presence of lactose, and quantitatively by the polariscope; a normal individual will eliminate about 90 per cent of the lactose in less than four or five hours; if glomerular function is impaired the lactose excretion is prolonged and a smaller amount of lactose may be recovered (Schlayer and Takayasu).

Potassium Iodid.—0.5 gm. of the drug is given by mouth; the urine is examined every two hours by Sandow's method; the average duration in normal persons necessary for excretion is 44 hours though no observation under 60 hours should be considered as indicating a delayed elimination (Schlayer and Takayasu). The dose of potassium iodid does not appear to have much bearing on the test, though it must be recognized that the various tests for the identification of potassium iodid in the urine vary much in their delicacy and that there is a large personal equation in judging of the absence or presence of slight amounts of iodid by means of any of these reactions. These factors may account for the wide variations in the normal elimination time for potassium iodid as described by different authors, the limits being 25 to 48 hours according to Rowntree and Fitz.

The Constituents of the Blood.

For the significance of sugar, cholesterol, calcium, phosphates, sodium chlorid, proteins and non-protein nitrogenous constituents of the blood reference is made to previous chapters in the section on nephritis.

The Coefficient of Urea Excretion

By means of a mathematical formula, which made use of the concentration of urea in the blood and urine, Ambard expressed the power of

the kidney to eliminate urea. This method of estimating renal function has given rise to many investigations; some of these have devoted themselves to the clinical application of Ambard's coefficient, others to the revision of Ambard's formula.

Ambard's Coefficient. (*Ambard, Ambard and Weill.*)—McLean(*a*) summarizes "Ambard's laws" regarding urea excretion as follows:

Ambard's first experiments were with dogs. He found that when the concentration of urea in the urine is constant the rate of excretion varies directly as the square of the concentration of urea in the blood. His first law thus formulated is:

$$\frac{(\text{Urea in blood})^2}{\text{Rate of excretion}} = \text{Constant, or } \frac{\text{Urea in blood}}{\sqrt{\text{Excretion per unit of time}}} = \text{Constant}$$

(when concentration in urine is constant).

Secondly, he found, by comparing different experiments in which the concentration of urea in the blood was the same, that the rate of excretion then varied inversely as the square root of the concentration in the urine; *i. e.*,

$$\frac{\text{Rate of excretion I}}{\text{Rate of excretion II}} = \frac{\sqrt{\text{Concentration II}}}{\sqrt{\text{Concentration I}}}$$

This may also be expressed

$$\text{Rate I } \sqrt{\text{Concentration I}} = \text{Rate II } \sqrt{\text{Concentration II}}$$

or, in other words, when the blood urea remains constant the rate times the square root of the concentration in the urine remains constant. Introducing this factor into the first law we have:

$$\frac{\text{Urea in blood}}{\sqrt{\text{Rate of excretion}}\ \sqrt{\text{Concentration in urine}}} = \text{Constant.}$$

This was shown to hold true for the same animal or for the same individual, or for animals or individuals of the same or nearly the same weight. For individuals of different weight it became necessary to introduce a further modification, in order to make all individuals comparable. This modification is based on the assumption, supported by the results of experiment, that, other factors remaining constant, the rate of excretion varies directly with the weight of the individual. One assumes that the amount of active kidney tissue and the circulation of blood through the kidneys vary directly with the weight. This may be expressed as

$$\frac{\text{Rate}}{\text{Weight}} = \text{Constant (other factors remaining constant).}$$

Introducing this correction into the previous formula, we have

$$\frac{\text{Concentration of urea in blood}}{\sqrt{\frac{\text{Weight}}{\text{Rate}}}\sqrt{\text{Concentration in urine}}} = \text{Constant.}$$

This formula expresses all of Ambard's laws in the simplest form. In order to standardize the formula for use in human subjects, it was expressed by Ambard as follows:

$$\frac{\text{Ur}}{\sqrt{\text{D} \times \frac{70}{\text{Wt}}} \times \sqrt{\frac{\text{C}}{25}}} = \text{K (constant).}$$

Ur = gm. of urea per liter of blood.
D = gm. of urea excreted per 24 hours.
Wt = weight of individual in kilos.
C = gm. of urea per liter of urine.

This formula is known as Ambard's coefficient, and the value obtained for K by Ambard and Weill in normal human subjects ranged beween 0.060 and 0.070.

The introduction of a standard weight of 70 kilos, a standard concentration of 25 gm. per liter, and the expression of rate of excretion as the rate per 24 hours are purely arbitrary, and can not affect the general relationship between the variable factors. When these arbitrary factors are kept constant, they, in conjunction with the constant relationship between the four variable factors, tend to keep K constant, and the actual numerical value of K is determined by these arbitrary additions to the formula. All the observations of the French school are based on the formula as thus stated.

McLean found the normal variations to be somewhat greater than Ambard and Weill, the usual normal being about 0.080. Lewis agrees with McLean in that he believes the coefficient to vary between 0.060 and 0.090 although his average is somewhat lower, being 0.074.

McLean's Coefficient.—In order to measure the rate of urea excretion in percentage of the normal standard, McLean(*a*) has derived a formula, from Ambard's figures, whose normal value is 100, the maximal range being between 80 and 250. *"McLean's index"* is as follows:

Substituting for K (Ambard's coefficient) and simplifying,

$$\text{Index} = \frac{\text{Gm. urea per 24 hrs.} \sqrt{\text{Gm. urea per liter of urine}} \times 8.96.}{\text{Wt. in kilos} \times (\text{Gm. urea per liter of blood})^2}$$

When K = 0.080, the standard normal, I (index of urea excretion) = 100.

or $$I = \frac{D\sqrt{C} \times 8.96}{Wt. \times Ur^2}$$

When values below 80 are noted the power of the kidney to excrete urea is correspondingly diminished.

The Coefficient of Austin, Stillman and Van Slyke.—The *"Urea-secretory constant"* of these authors is:

For Normal Man:

$$K = \frac{D}{B\sqrt{V\,W}} = 7.5 \pm 3$$

D = Urea output (grams per 24 hour time unit)
B = Blood urea (grams per liter)
V = Volume output (liters per 24 hour time unit)
W = Body weight (kilos)

When values below the minimum normal of 4.5 are noted, the urea excreting function is deficient.

The urea-secretory constant for normal persons is probably more nearly correct than Ambard's formula. Its clinical worth remains to be tried out. Judging from the successful application of Ambard's constant, it promises to be of great importance. Austin, Stillman and Van Slyke believe that their "urea-secretory constant" is an equation of definitely greater accuracy than Ambard's. However, they do not consider their conclusions a disproof of Ambard's work but rather an advance which has proceeded along the path opened by his researches. A résumé of their reasoning is contained in the subsequent section.

Facts Regarding Renal Function That Have Been Developed by a Study of the Laws of Urea Excretion

The Effect of Concentration of Urea in the Blood on the Quantity of Urea Excreted by the Kidneys.—It is a matter that admits of no doubt that, other factors remaining constant, the amount of urea put out by the kidneys in a given unit of time increases as the blood urea rises. The exact proportion of these values to one another has been a matter of considerable dispute. Ambard believed that the rate of urea excretion varied proportionately to the square of urea in the blood. Subsequent investigators seem to agree that the ratio is a much more simple one, namely, that the rate of urea excretion is directly proportional to the concentration of urea in the blood (Addis, Barnett and Shevky, Addis and Watanabe(*c*), Austin, Stillman and Van Slyke, Marshall and Davis, Pepper and Austin(*b*)). According to them the equation would be:

$$\frac{\text{urea in the blood}}{\text{rate of urea excretion}} = \text{constant.}$$

whereas Ambard formulates these factors as follows:

$$\frac{(\text{urea in the blood})^2}{\text{rate of urea excretion}} = \text{constant.}$$

A consideration of all the facts presented makes it seem probable that the first ratio is more nearly correct.

The Relation of Water Elimination to Urea Excretion.—It has been definitely established that an increased urine volume in a given unit of time, that is a diuresis, will increase the total output of solids in the urine. It remained for Austin, Stillman and Van Slyke to determine the limitations of this phenomenon. They found that an increase in the rate of urine volume excretion up to a certain point varying between 2.5 to 6.0 liters in twenty-four hours result in a regular increase of urea output which surpasses the rate which would be expected from the blood urea. In other words, the ratio $\frac{\text{rate of urea excretion}}{\text{urea in the blood}}$ rises as the urine volume increases. Quantitatively this increase is approximately proportional to the square root of the rate of urine volume excretion or

$$\frac{\text{rate of urea excretion}}{\text{urea in the blood}} = \text{constant } \sqrt{\text{volume of urine.}}$$

There is a limit beyond which a greater urinary flow will not increase the urea elimination. This has been well termed the *augmentation limit.* The augmentation limit is not the same in every individual. It varies from 2.5 to 6.0 liters in twenty-four hours in normal persons. Its value, when applied to renal affections, remains to be determined. Such 24 hour urinary volumes (2.5 to 6 liters) are in excess of the urinary volume usually observed in man. On the other hand, a marked lowering of the urinary flow, as occurs in dehydration, will diminish the urea output (Marshall and Davis). If anuria results, because of fluid loss through other emunctories than the kidneys, as in cholera, the rather curious phenomenon is presented of absolute cessation of kidney activity while there is no impairment of renal function, as far as the kidneys themselves are concerned.

The Concentration of Urea in the Urine.—Austin, Stillman and Van Slyke claim that the concentration of urea in the urine has no definite constant influence on the rate of urea excretion; it only becomes of importance when the urinary volume is low. The urine volume appears to be the determining factor as shown in the previous paragraph. Under certain common pathological conditions, when the ability of the kidney to concentrate the urine is markedly diminished, it is found that the urine volume is the absolute controlling factor in the amount of urea excreted inasmuch as the urinary urea concentration remains more or less constant. Addis and Watonabe in their various publications have stressed the independence of the value of Ambard's constant from the

concentration of urea in the urine. Hence Ambard's second law (see section on Ambard's constant) is not correct in the view of later researches.

The Reliability of Coefficients of Urea Excretion.—Jonas and Austin express their skepticism concerning the precision of the Ambard coefficient. In the later constant of Austin, Stillman and Van Slyke, the most obvious mistakes of Ambard's work have been corrected. However, even these recent investigators, in elucidating their improved equation, tell us that other factors than those represented in their formula may modify the value of the constant. They mention "nervous" or "hormone" influences. It is undoubtedly true that no test, applied to human function, possesses absolute mathematical accuracy. It will always require a great deal of clinical judgment and experience to properly evaluate any procedure of this sort. That the coefficient of urea excretion is particularly susceptible to influences for which no allowances can be made in a routine formula is very obvious.

Method of Determining the Coefficient of Urea Excretion.—A time is chosen which is as long as possible after the ingestion of food. This will tend to produce a comparatively constant level of urea in the blood. The patient drinks about 200 c.c. of water in order to insure an adequate flow of urine; one-half hour later, the bladder is emptied and the urine subsequently collected after an accurately timed interval. This should not be longer than two hours, and by preference this period should be shorter. The blood is collected midway between the two voidings that demark the urinary specimen which is to be analyzed. The urea is determined in the blood and urine; the urine is measured and calculations are made to increase it to a 24 hour basis; the figures are then substituted in the formulas previously given and the coefficient obtained.

The Clinical Value of the Coefficient of Urea Excretion.—Thus far the application of the coefficient to patients has only been with Ambard's constant or its modification, the McLean Index. Hence the conclusions which follow have no other basis. The urea-secretory constant of Austin, Stillman and Van Slyke awaits its clinical christening.

In general the coefficient of urea excretion may be regarded as paralleling the progress of acute or chronic renal disease fairly well; it seems to fall in line, in the majority of cases, with the phthalein test. Its main point of value appears to be that in those cases with impaired kidney function that have their blood urea reduced to a normal level, the coefficient will nevertheless show subnormal values and thus indicate the true state of affairs (Lewis, McLean(*a*), Ambard, and Widal, Weill and Vallery-Radot). On the other hand, Jonas and Austin believe that this method of testing renal function affords "no information of diagnostic or prognostic value that could not be as readily deduced from the blood urea alone." This is true to a certain degree. Whether the new "urea-secretory constant" will obviate some of the faults in the older formula re-

mains to be determined. In many cases the coefficient of Ambard is of very great help; it is not infallible and it is a test that requires much time and painstaking attention to detail.

It is found that the coefficient of urea secretion shows better than normal figures in fever, hyperthyroidism, and in the early stages of chronic nephritis. Lewis attributes these in part to increased metabolic activity of the kidney and other tissues, characteristic of fever and augmented thyroid secretion, and in part to the irritability of the kidney which, according to Schlayer, is a sign of slight involvement of the kidney. These facts concerning Ambard's constant are paralleled by similar findings in regard to phthalein and water excretion.

It is interesting to note from Lewis' work how in very severe nephritis the coefficient of urea excretion is modified by one predominating influence, the amount of water excreted, and is largely independent of the concentration of urea in the blood. In the far advanced cases of chronic Bright's disease the concentration of urea in the urine is often an absolutely fixed quantity regardless of the volume of urine or of the level of the blood urea. Under these circumstances it becomes obvious that Ambard's Constant will vary:

(1) directly as the blood urea (when the urea concentration in the urine and volume of urine both remained fixed)
(2) indirectly as the volume of urine (the urea concentration in the urine remains fixed, but the urinary volume varies)

Lewis demonstrates some beautiful examples of these possibilities. Under these circumstances, it is evident that the volume of urine is the last compensating factor to give way as renal insufficiency progresses. This is extremely important to bear in mind from the therapeutic point of view when treating the symptom complex of retention of waste products in nephritis.

The Chlorid Threshold in Nephritis

Ambard and Weill formulated certain laws by which they estimated the chlorid threshold of the kidneys. These have been interpreted by McLean(*a*) as follows: "Ambard and Weill applied laws to the excretion of sodium chlorid in human subjects. They found that the same general laws were applicable to sodium chlorid and to urea, with the important exception that, while excretion of urea occurs no matter how low its concentration in the blood falls, there is a threshold for chlorid excretion, and when the concentration in the plasma falls below this threshold value, excretion of chlorid practically ceases. In view of the fact that there is a wide difference in chlorid content of the corpuscles and plasma, plasma alone, as the fluid part of the blood, has been studied. Ambard and Weill,

partly by direct experiment and partly by plotting curves, established the normal threshold value for sodium chlorid as 5.62 gm. per liter of plasma. Therefore the sodium chlorid above 5.62 gm. per liter determines the rate of excretion, and the law may be expressed as for urea.

$$\frac{\text{Excess NaCl over 5.62 gm. per liter of plasma}}{\sqrt{\frac{\text{NaCl in 24 hrs.}}{\text{Wt. in kilos}}}\sqrt{\text{NaCl per liter of urine}}} = \text{Constant.}$$

For practical use it appears best to calculate the plasma sodium chlorid from the rate of excretion, and to compare the calculated concentration with that actually found. The formula, as derived with the use of values actually found for the constant in the above formula, reads

$$\text{Plasma NaCl} = 5.62 + \sqrt{\frac{D \times \frac{70}{Wt}\sqrt{\frac{C}{14}}}{79.93}}$$

(The symbols have the same meaning as in the urea formulas. See section on the coefficient of urea excretion).
This, in its simplest form, reads

$$\text{Plasma NaCl} = 5.62 + \sqrt{\frac{\text{Gm. NaCl per 24 hrs.} \sqrt{\text{Gm. NaCl per liter of urine.}}}{4.23 \times \text{Wt. in kilos}}}$$

The constancy of this formula depends on two factors: (1) the constancy of the threshold, and (2) the constancy of the rate of excretion of sodium chlorid above the threshold. In their original contribution Ambard and Weill believed that the threshold was quite constant in normal individuals. Later they recognized some variation in the threshold in normal individuals, though this variation seems to be relatively slight. Assuming that the laws for rate of excretion of sodium chlorid over the threshold remain constant in normal individuals, one may calculate the threshold by subtracting the calculated excess from the sodium chlorid actually found in the plasma, and our figures for the variations in the threshold are based on the following formula:

$$\text{Threshold} = \text{Plasma NaCl} - \sqrt{\frac{D\sqrt{C}}{4.23\ \text{Wt.}}}$$

This formula is subject to error if the rate of excretion over the threshold varies. We have not yet found that the urea excretion gives any basis for estimating the rate of sodium chlorid excretion, and accordingly have not used Ambard's combined formula for calculating the threshold of sodium chlorid excretion. Our figures on the threshold are only to be regarded as approximate, since we have so far no means of recognizing variations in rate of excretion over the threshold.

The principles of the laws of urea and chlorid excretion may be illus-

trated in a very simple way. If we imagine a vessel into which water flows at a constant rate, escaping through an outlet at the bottom, the water will seek the level in the vessel at which the pressure is such that the rate of outflow is exactly equal to the intake. If we then increase or decrease the rate of inflow, the level will change to meet the new conditions. The change in level of the fluid in the vessel may be regarded as a compensatory change. Under physiological conditions fluctuations in the level of blood urea compensate for changes in the rapidity of formation of urea, and changes in the level of chlorid in the plasma compensate for fluctuations in chlorid intake. Under pathological conditions changes in the level of urea and sodium chlorid in the blood also occur to compensate for changes in the outlet, in the form of diseased kidneys. In the case of chlorids the outlet of the vessel must be considered as being at some distance from the bottom, and in such a case only the level of fluid above the outlet would play any part in determining the rate of outflow, which would cease when the level of fluid fell to the level of the outlet. Similarly, only the chlorid above the threshold determines the rate of excretion, which practically ceases when the threshold value is reached."

McLean, as the result of his observations, finds the chlorid threshold to be of considerable value; his reasoning concerning the underlying theory, which he evidently credits with the possibility of clinical application, is as follows: "It is manifestly wrong to consider the kidneys responsible for the failure to excrete a certain amount of salt given by mouth, if the salt is taken up by the tissues and the concentration in the plasma remains low. But if the concentration of chlorids in the blood or plasma remains proportionately high, and the rate of excretion proportionately low, it is correct to speak of retention in the sense of a failure to excrete properly. This is the condition in certain types of cardiorenal, or renal disease." He observed that the plasma chlorids were high in certain forms of cardiac and renal disease, and edema; it was low in pneumonia, fever, diabetes or as the result of the action of diuretics (digitalis).

On the other hand Atchley believes from his experience with eight cases of acute nephritis that: "In no case was the rate of excretion dependent on the concentration of chlorids in the plasma. This much is clear; there is no definite constant threshold for any individual nor is the height of the threshold an index of the degree of impairment of chlorid function. More valuable than what the formula expresses are the facts that may be gathered from a determination of the plasma chlorid concentration, together with a knowledge of the daily intake and output of salt. There are fairly conclusive grounds for saying that an abnormally high plasma chlorid on a moderate salt intake may be the only evidence of a latent disturbance of chlorid metabolism."

It is obvious that in the face of such contradictory opinions concerning the value of the kidney threshold for chlorids, many more observations

will be necessary before the formula may be considered to be on a satisfactory basis. It is probable that there is a good deal to be said for it, but that it must be perfected in certain details before it can be accepted as a standard clinical procedure; a similar stormy course has marked the career of Ambard's coefficient for urea excretion.

What other investigators have said concerning this equation may be of interest. Wolferth notes that the normal sodium chlorid of the plasma is 5.56 to 6.17 gm. per liter; in passive congestion it rises as high as 6.69 and in nephritis to 6.40, and that the renal threshold for chlorids is raised in the two latter states; he finds that an elevated plasma chlorid threshold is valuable evidence of the existence of a nephritis when circulatory disturbances can be excluded. O'Hare believes that the index of sodium chlorid excretion is of importance when the blood chlorids are normal. Austin and Jonas, on the basis of experiments, came to the conclusion that in normal animals the chlorid index holds true, but that in nephritis (uranium) "there may be an alteration in the threshold, or a disturbance in the degree of renal response to increments in the plasma chlorids above the threshold. Because of these two variables, interpretation of the significance of alterations in the chlorid index of pathological cases is complicated."

Tests for Urea and Salt Excretion

Monakow(*a*) (1911) following the ideas of French clinicians suggested the addition of 10 gm. of salt and 20 gm. of urea to a patient's dietary. O'Hare(*a*) (1916) described the procedure as follows: "The 'added urea and salt test' has been carried out much as described by von Monakow. Our patients have been placed on a diet containing 75 mg. of protein, 4 gm. of sodium chlorid and 1,500 c.c. of water with caloric value of 2,000 to 2,200. After the output of fluid, salt and nitrogen reaches an equilibrium on this diet, on one day 10 gm. of additional salt is given, and several days later the patient receives 20 gm. of urea. This order may be reversed. The daily output of urine, salt and nitrogen is determined and charted." Then O'Hare goes on to voice his impressions concerning these tests: "After salt or nitrogen are added to the diet in normal individuals their excretion after forty-eight hours return to its previous level. In the diseased kidney this may not be the case. Sometimes the added salt or urea produces a diuresis and this disturbs the elimination of both salt and nitrogen, the increased water output carrying out with it more salt or nitrogen. Consequently it is desirable to observe the effect of each added substance for several days after it is given before introducing the other. Then it often takes several days on the diet before salt, nitrogen and water excretion reach an approximately constant rate of excretion. These several factors render it desirable to prolong the added urea and salt test over a period of ten or twelve days, and in some cases even longer.

The added urea and salt test gives us rather early evidence of disturbed nitrogen and salt elimination of the kidney, as shown by delayed and deficient excretion of these substances. Simple, logical and direct as it seems, the test has many practical difficulties. In the ten or twelve days needed to carry it out the patient may tire of the hospital and refuse to stay; changes in the patient's condition may necessitate a change in diet or other interference with the conditions under which the experiment is being carried out; a woman may begin to menstruate; portions of the urine may be lost unavoidably as when the patient voids at stool, etc.; or the diet may become very monotonous. Sometimes, especially during the formation of edema, there may be a storing up of nitrogen or salt with a subsequent discharge of the same either just before or coincidently with the giving of the added urea or salt. This of course interferes with the correct interpretation of the changes in the excretion curves. Urea taken by mouth sometimes causes a diarrhea, with consequent probable loss of an unknown amount of nitrogen in the feces. This would have the effect of showing an apparently lower nitrogen excretion than the kidneys are really capable of handling. Of course variations in rate and completeness of absorption from the gastro-intestinal tract introduce possible errors in such dietary tests. Tissue retention, especially of salt, is another possible source of error in any such test."

It becomes clear from the above that there are many factors besides the condition of the kidney which may influence the excretion of urea and salt and that simply adding them to the food and determining the quantity excreted may not yield the information desired concerning the kidney function (see nitrogen balance in nephritis and tests for function of the glomeruli and tubules). It is comparatively simple theoretically to judge of these tests when there is either an adequate elimination of the added urea or salt or a straightforward retention of these substances (see Table 25).

TABLE 25

SALT EXCRETION TEST IN A NORMAL PERSON AND IN A CASE OF SECONDARY CONTRACTED KIDNEY; DELAYED EXCRETION OF SALT AND POLYURIA OCCURS IN THE NEPHRITIC PATIENT. (Munk)

Normal				Secondary Contracted Kidney			
Day	NaCl Grams		Urine Vol. c.c.	Day	NaCl Grams		Urine Vol. c.c.
	Intake	Urine			Intake	Urine	
1	9	8.5	1385	1	10	10.2	2810
2	9	9.2	1340	2	10	9.3	2290
3	9	8.8	1455	3	20	17.0	3275
4	19	16.9	1832	4	10	10.5	2930
5	9	10.8	1655	5	10	15.7	4130

Some of the usual as well as the bizarre findings developed during the course of these methods may be cited:

Munk, after adding 10 grams of salt to the diet of a patient, found that the urine volume dropped from 1550 to 750 c.c. and the sodium chlorid elimination from 8.2 grams to 3.1 grams. The author has seen such a paradoxical effect on several occasions. The reciprocal relation between urea and sodium chlorid noted by Zondek(*b*) is very interesting; on giving urea the sodium chlorid excretion diminished and vice versa (see Table 26).

TABLE 26

THE INGESTION OF UREA MAY RESULT IN A DEPRESSION OF SALT EXCRETION AND VICE VERSA. (Zondek(*b*))

Urinary Output per Day, Grams		Test Substance Added to Diet
Sodium Chlorid	Nitrogen	
5.0	11.0	
6.0	9.0	
4.2	8.0	Urea, 20 gm.
7.0	13.0	
2.0	12.0	
8.0	9.0	
7.0	7.0	
6.0	9.0	
7.0	8.0	
7.5	9.0	
8.0	10.0	
9.0	11.0	Salt, 10 gm.
14.0	7.0	
13.0	6.0	
10.0	11.0	

It becomes obvious that the tests for salt and urea excretion as proposed are cumbersome, are a severe strain upon the patient, and do not yield clear cut results. They may be of interest and value especially from the pathologico-physiological point of view, but they do not yield the information which blood chemistry does in regard to the ability of the kidney to keep the body clear of waste products, nor do they furnish as good data as the test day for renal function concerning the mode of excretion of urea or sodium chlorid.

Test Day for Renal Function

This procedure has been variously called the nephritic test meal, test meal for renal function, two hour renal test or two hour test. Inasmuch as no set diet is required and the specimens of urine need not be collected in two hour intervals, the author has preferred to resort to the name of test day for renal function. As this method of observation has been developed it has come to include an estimation of the adequacy and suitability of the patient's habitual food and fluid intake to his needs and their effect upon the kidneys. Therefore it is believed that the term test day for renal function meets the situation better than the others mentioned above.

When this test was first conceived by Hedinger and Schlayer, it was supposed that a full dietary containing a reasonable amount of fluids, salt and purins was necessary to obtain a "Normal response" on the part of the kidney. Accordingly they designed an elaborate series of meals. Mosenthal(*b*) (1915) modified their procedure to meet American standards of three meals a day; the outline giving directions for the diet and collections of urinary specimens at the time were the following:

TEST DAY FOR RENAL FUNCTION

For ..... Date .....

All food is to be *salt free.*

Salt for each meal will be furnished in weighed amounts.*

All food or fluid not taken must be weighed or measured after meals and charted in the spaces below.

Allow no food or fluid of any kind except at meal times.

Note any mishaps or irregularities that occur in giving the diet or collecting the specimens.

Breakfast, 8 a. m.

Boiled oatmeal, 100 gm.....
Sugar, 1-2 teaspoonfuls.....
Milk, 30 c.c.....
Two slices bread (30 gm. each).....
Butter, 20 gm.....
Coffee, 160 c.c. } 200 c.c.....
Sugar, 1 teaspoonful } .....
Milk, 40 c.c. } .....
Milk, 200 c.c.....
Water, 200 c.c.....

Dinner, 12 Noon.

Meat soup, 180 c.c.....
Beefsteak, 100 gm.....
Potato (baked, mashed or boiled), 130 gm.....
Green vegetables, as desired.....
Two slices bread (30 gm. each).....
Butter, 20 gm.....
Tea, 180 c.c. } 200 c.c.....
Sugar, 1 teaspoonful } .....
Milk, 20 c.c. } .....
Water, 250 c.c.....
Pudding (tapioca or rice), 110 gm.....

Supper, 5 p. m.

Two eggs, cooked in any style.....
Two slices bread (30 gm. each).....
Butter, 20 gm.....
Tea, 180 c.c. } .....
Sugar, 1 teaspoonful } 200 c.c.....
Milk, 20 c.c. } .....
Fruit (stewed or fresh), 1 portion.....
Water, 300 c.c.....

8 a. m.—No food or fluid is to be given during the night or until 8 o'clock the next morning (after voiding), when the regular diet is resumed. Patient is to empty bladder at 8 a. m. and at the end of each period, as indicated below. The specimens are to be collected for the following periods in properly labeled bottles:

8 a. m.-10 a. m.; 10 a. m.-12 n.; 12 n.-2 p. m.; 2 p. m.-4 p. m.; 4 p. m.-6 p. m.; 6 p. m.-8 p. m.; 8 p. m.-8 a. m.

* One capsule of salt, containing 2.3 gm. of sodium chlorid, is furnished for each meal. The salt which is not consumed is returned and weighed, and the actual amount of salt taken is calculated.

The above dietary contains approximately 13.4 gm. of nitrogen, 8.5 gm. of salt, 1,760 c.c. of fluid, and a considerable quantity of purin material in the meat, soup, tea and coffee.

This method of carrying out the test was found to be rather laborious. Later observations by Schlayer and Beckman, and Mosenthal(*c*)(1918) showed that, except for certain minor differences, no real discrepancies existed in the results obtained, whether the diet contained so-called diuretic substances (purins, sodium chlorid, etc.) or not. In fact Mosenthal (1918) demonstrated that variations in the volume of urine and specific gravity occurred even when no food, but water only was taken, at two hourly intervals, and the urine was collected every two hours. It appears that the kidney in excreting water acts much on the principle of a syphon. It requires a certain amount of fluid to start a diuretic flow, which, when once begun, continues, even after the excess of water eliminated is greater than the amount of fluid taken, that has stimulated the kidney to increased activity. It becomes obvious therefore that diet is of minor importance in carrying out the test day for renal function. Under the circumstances it appeared feasible to allow the patient to continue his or her normal diet (with the exception of forbidding food or fluid after supper until the next breakfast) while the test was carried out. This has an additional advantage inasmuch as the individual's reaction to the usual diet and environment can be taken into consideration and any abnormality in renal function may be met by intelligently directed therapeutic measures. The directions given the patient are these:

DIRECTIONS FOR "TEST DAY FOR RENAL FUNCTION"

Eat and drink what you are accustomed to but be sure that neither food nor drink is taken after supper until the test is completed. Note time and approximate amounts of food and fluid taken at each meal.

8.00 A.M. Void urine and discard the urine.
8.00 A.M. Eat breakfast.
10.00 A.M. Void urine and place all in a labeled bottle.
12.00 noon Void urine and save as before.
1.00 P.M. Eat lunch.
2.00 P.M. Void urine and save as before.
4.00 P.M. " " " " " "
7.00 P.M. " " " " " "
7.00 P.M. Eat supper.
10.00 P.M. Void urine and save as before.
All urine voided after 10.00 P.M. until 8.00 A.M. is to be placed in a bottle labeled 8.00 A.M.
8.000 A.M. Void urine and place in the bottle labeled 8.00 A.M.

The criteria for judging of the efficiency of the kidney by means of this test are:

1. The variation of the specific gravity in the different specimens of urine collected.
2. The maximal specific gravity attained by any specimen.
3. The quantity of night urine.
4. The concentration of sodium chlorid, urea, or total nitrogen in any of the specimens.
5. The total quantity of sodium chlorid, urea or total nitrogen eliminated.

The degrees of variation of the specific gravity from the highest to the lowest value obtained in the normal individual is 9 or more. An example of this is given in Table 27.

TABLE 27

EXAMPLE OF NORMAL RESULT WITH TEST DAY FOR RENAL FUNCTION. NOTE THE VARIATIONS IN THE SPECIFIC GRAVITY, LOW AMOUNT OF NIGHT URINE, THE VARIATIONS IN THE CONCENTRATION OF SALT AND NITROGEN, AND THE RISE OF THE CONCENTRATION OF SALT AND NITROGEN TO MORE THAN ONE PER CENT IN CERTAIN SPECIMENS. (IN THE ROUTINE PERFORMANCE OF THE TEST THE SALT AND NITROGEN, OR UREA NEED NOT BE DETERMINED IN EVERY SPECIMEN AND MAY BE OMITTED ENTIRELY IF THEY YIELD NO DESIRED INFORMATION.) (Mosenthal, 1915.)

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent	Gm.	Per Cent	Gm.
8-10	153	1.016	1.32	2.02	0.89	1.26
10-12	156	1.019	1.25	1.95	0.74	1.15
12- 2	194	1.012	0.64	1.24	0.59	1.14
2- 4	260	1.014	0.77	2.00	0.56	1.46
4- 6	114	1.020	0.99	1.13	0.95	1.08
6- 8	238	1.010	0.43	1.02	0.52	1.23
Total day	1,115	.....	....	9.36	....	7.32
Night, 8-8	375	1.020	0.63	2.36	1.23	4.61
Total 24 hours	1,490	.....	....	11.72	....	11.93
Intake	1,760	.....	....	8.50	....	13.40
Balance	+270	.....	....	—3.22	....	+1.47

Under certain circumstances, if too little water is taken, or in very hot weather when the fluid excretion of the urine is diminished because of loss of water in other directions, the variations in the specific gravity may be lower than normal and it may be fixed at a somewhat higher level. This has been stressed by Lyle and Sharlit. An example of this sort is given in Table 28.

TABLE 28

A Case in Which a High, Somewhat Fixed Specific Gravity is Due to an Inadequate Fluid Intake; the Low Chlorid and Urea Output Indicate That the Patient is on an Insufficient Diet for the Proper Maintenance of Nutrition; the Test Was Carried Out While the Patient Was Taking Her Customary Diet

Time	c.c.	Sp. Gr.	NaCl		Urea	
			%	Gms.	%	Gms.
8-10	40	1021				
10-12	66	18				
12- 2	95	18				
2- 4	58	21				
4- 7	64	20				
7-10	118	17				
Total day	441		.60	2.65	.64	2.8
10-8	198	22	.48	0.95	2.22	4.4
Total	639			3.60		7.2

Mrs. E., Age 28, Blood Pressure 126/78.

Blood Sugar .10 per cent, Urea N 9.9 mg. per 100 c.c., Uric Acid 2.9 mg. per 100 c.c.

Urine Trace of albumin, a few pus cells, an occasional red blood cell.

Diagnosis Renal calculus.

Renal Function Normal.

Metabolism Fluid, sodium chlorid and protein intake low.

It is probable that there should be a variation of at least nine points in the specific gravity readings if the kidney is to be permitted to act at its maximal efficiency. In this case, therefore, it is decidedly indicated that more fluid should be taken with the food.

When the kidney becomes insufficient, one of the first signs to manifest itself is the inability to void a concentrated urine. Any retention which might occur because of this is compensated for by an increase in the urine volume. If the ability to produce a polyuria is practically without limit, there will be no evidences of lack of elimination of the solids. This is very well illustrated in diabetes insipidus. In this disease there is no diminution of renal function, according to any of the tests, except that a polyuria and a very low and fixed specific gravity exist. Even though the phthalein elimination be perfect and there is no accumulation of the waste products in the blood, yet there is loss of one very distinct function of the kidney, that of the power of concentration. Under such circumstances, when one test for renal function does not tally with the remainder, it has been customary, on the part of some investigators, to condemn one or the other of these procedures as being worthless. In the heat of the argument it is often forgotten that tests based on physiological processes must have a definite meaning if the knowledge is at hand to interpret them

TABLE 29

SHOWING THE VARIATIONS OF SPECIFIC GRAVITY READINGS IN DIFFERENT DISEASES WITH THE TEST DAY FOR RENAL FUNCTION. (Mosenthal, 1915)

Case	Specific Gravity *						Degrees of Variation in Readings
Normal	16	19	12	14	20	10	10
Incipient primary contracted kidney	09	14	09	10	14	06	8
Incipient primary contracted kidney	18	09	16	22	13	10	13
Advancing primary contracted kidney	18	17	13	13	13	15	5
Advancing primary contracted kidney	19	20	20	20	21	20	2
Advanced primary contracted kidney	11	11	10	11	11	11	1
Advanced primary contracted kidney	12	11	11	11	12	13	2
Advanced primary contracted kidney	10	09	10	09	09	10	1
Advanced primary contracted kidney	05	06	07	08	..	08	3
Incipient chronic diffuse nephritis	25	..	24	33	28	30	9
Incipient chronic diffuse nephritis	09	16	15	17	12	07	10
Advanced chronic diffuse nephritis	12	11	14	11	13	11	3
Secondary contracted kidney	09	10	12	10	12	10	3
Congested kidney; myocardial decompensation marked	18	20	19	18	20	21	3
Congested kidney; moderate myocardial decompensation	25	24	24	25	24	21	4
Congested kidney; cardiac compensation; losing edema	12	15	10	15	13	10	5
Congested kidney; cardiac compensation; edema disappeared	05	06	11	09	09	10	6
Polycystic kidney	10	10	10	11	10	10	1
Marked anemia	10	10	10	10	10	11	1
Diabetes insipidus	04	04	06	04	04	04	2
Cystitis, pyelitis, prostatic hypertrophy	10	10	10	10	11	11	1
Pyonephrosis	11	12	12	13	12	12	2

* Last two figures only.

correctly. It must also be remembered that the activity of the kidney is composed of different functions, that to a certain degree act independently of one another; it is well known, for instance, that the power to excrete salt and urea is not synchronously curtailed in a great many cases; but to claim that a study of either one is of no importance because the elimination of the other does not parallel it, is obviously absurd.

When renal function becomes impaired the specific gravity tends to become fixed, that is, instead of a variation of 9, there may be only a difference of one or two points. (Table 29.) In only two conditions, excepting the normal individual with an inadequate water intake, is a high fixed specific gravity found; these are passive congestion and certain cases of nephritis accompanied by albuminuria and edema. It is very satisfactory to note that on chemical examination of the urine these cases can usually be identified because of the high concentration of nitrogen and the low percentage of sodium chlorid present in the urine. An example is given in Table 30.

TABLE 30

TEST DAY FOR RENAL FUNCTION IN A PATIENT SUFFERING WITH CARDIAC DECOMPENSATION. NOTE THE HIGH FIXED SPECIFIC GRAVITY, THE GOOD CONCENTRATION OF NITROGEN AS COMPARED TO THE LOW FIGURES FOR SALT. SOMEWHAT SIMILAR RESULTS MAY BE OBTAINED IN SOME CASES OF NEPHRITIS COMPLICATED BY EDEMA. (Mosenthal, 1915)

Time of Day	Urine c.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent	Gm.	Per Cent	Gm.
8-10	61	1.018	0.20	0.12	1.52	0.93
10-12	52	1.020	0.24	0.12	1.83	0.95
12- 2	65	1.019	0.26	0.17	1.73	1.12
2- 4	55	1.018	0.27	0.15	1.65	0.90
4- 6	30	1.020	0.26	0.07	1.61	0.48
6- 8	35	1.021	0.40	0.14	1.80	0.63
Total day	298	.....	....	0.77	....	5.01
Night, 8-8	275	1.021	0.31	0.85	1.85	5.07
Total 24 hours	573	.....	....	1.62	....	10.08
Intake	570	.....	....	5.00	....	12.00
Balance	—3	.....	....	+3.38	....	+1.92

There are many extrarenal factors and disturbances of the urinary tract besides Bright's disease (see Table 29) that may be responsible for a diminished ability of the kidney to concentrate the urine. However, if renal function is to be measured by the quantity and the quality of urine eliminated at the urethra, these facts must be considered. Such diseases and conditions are cystitis, pyelitis, anemia (see Christian for special work on this subject), hypertrophied prostate, urethral stricture, polycystic kidney, elimination of edema, diabetes insipidus, paralysis of the bladder, as in tabes, and others. It becomes clear that clinical judgment must be applied to this as well as other tests for renal function if they are to be properly valued. In Table 31 the sudden changes that may occur as the result of extrarenal factors that control the formation of edema in nephritis are shown. Within less than an hour apparently the condition of oliguria and high specific gravity, which had persisted for several months, changed to one of polyuria and low specific gravity which continued on the succeeding days.

The *maximal specific gravity* attained in any specimen of urine on the test day for renal function, if the power of the kidney to concentrate is normal, is 1.020 or higher. The causes for the diminution in the specific gravity have already been mentioned in the preceding paragraphs under the heading of degrees of variation of the specific gravity, and need not be repeated here.

Nocturnal Polyuria.—One of the earliest signs of renal insufficiency is a nocturnal polyuria or nycturia (Quincke(*a*), v. Leube, Runeberg(*a*), Wilson, Iljisch, Laspeyeres, Pehu). If a normal person takes no food or

fluid after supper until the next breakfast and collects the urine for a period beginning three hours after the evening meal until just before breakfast the following morning, that is, for about ten hours, the quantity of urine voided is usually 400 c.c. or less (Mosenthal(*b*), 1915), though it may be as high as 750 c.c. (Lyle and Sharlit, Mosenthal(*c*), 1918). An amount between 400 and 750 c.c. may be regarded with suspicion; a night urine exceeding 750 c.c. is definitely pathological. A nycturia is found not only in nephritis but in a number of other conditions, that must not be confounded with Bright's disease: cystitis, hypertrophied prostate, urethral stricture, pyelitis, anemia, polycystic kidney, elimination of edema, diabetes or diabetes insipidus. Nocturnal polyuria occurs when renal function is impaired for two reasons; first, and this is the more common

TABLE 31

RESULTS WITH THE TEST DAY FOR RENAL FUNCTION IN A CASE OF ACUTE NEPHRITIS WITH EDEMA. THE EDEMA HAD PERSISTED FOR ABOUT FOUR MONTHS. ON THE FIRST DAY THE VERY SUDDEN CHANGE TO POLYURIA WITH A MUCH LOWERED SPECIFIC GRAVITY MAY BE NOTED. THE SUCCEEDING TEST SHOWS HOW THE ELIMINATION OF EDEMA IS CONTINUING. SUCH CHANGES ARE RESPONSIBLE FOR VERY VARIABLE RESULTS IN ACUTE NEPHRITIS; IT IS OBVIOUS, HOWEVER, THAT THEY ARE OF GREAT IMPORTANCE. (Mosenthal, 1918)

Time of Day	C.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent	Gm.	Per Cent	Gm.
8-10	102	1.017	0.89	0.91	0.50	0.51
10-12	90	1.020	0.83	0.75	0.68	0.61
12- 2	98	1.020	0.63	0.62	0.78	0.76
2- 4	118	1.021	0.47	0.55	0.81	0.96
4- 6	88	1.020	0.42	0.37	0.88	0.77
6- 8	390	1.006	0.17	0.66	0.26	1.01
Total day	886	.....	....	3.86	....	4.62
Night, 8-8	1,280	1.010	0.49	6.26	0.38	4.86
Total 24 hours	2,166	.....	....	10.12	....	9.48
Intake	1,760	.....	....	8.50	.....	13.40
Balance	—406	.....	....	—1.62	....	+3.92

Time of Day	C.c.	Sp. Gr.	Sodium Chlorid		Nitrogen	
			Per Cent	Gm.	Per Cent	Gm.
8-10	355	1.010	0.66	2.34	0.20	0.71
10-12	195	1.014	0.90	1.76	0.34	0.66
12- 2	290	1.011	0.64	1.86	0.28	0.81
2- 4	225	1.014	0.77	1.73	0.35	0.79
4- 6	180	1.014	0.89	1.60	0.37	0.67
6- 8	275	1.010	0.58	1.60	0.31	0.85
Total day	1,520	.....	....	10.89	....	4.48
Night, 8-8	1,660	1.010	0.60	9.96	0.21	3.49
Total 24 hours	3,180	.....	....	20.85	....	7.97
Intake	680	.....	....	8.50	....	3.89
Balance	—2,500	.....	....	—12.35	....	—4.08

cause, an inability of the kidney to eliminate sufficient solids during the daytime as to make the night an interval of comparative rest and inactivity; second, when edema exists and a period of elimination and polyuria has set in which persists day and night. The excess of water voided at night occurs partly because there is a residue of solid material to be excreted, partly because the power to concentrate the urine at higher levels has been lost, and in other instances (eliminating edema) because there is an excess of fluid furnished the kidney for excretion. Nocturnal polyuria usually (except in the patients who are in the process of ridding themselves of edema) means that the patient is taking an amount of food which his kidneys must excrete by an abnormal degree of effort. By changing the diet to one of a lower level of protein (for it is the end-products of protein, as well as the water and salts that are excreted in the urine, whereas the substances resulting from the digestion of carbohydrates and fats are excreted through other channels) the nocturnal polyuria is often set aside.

Thus in a series of 21 patients (see Table 32) with nocturnal polyuria on either a low or a moderately high protein diet there were 19 whose high

TABLE 32

COMPARISON OF NIGHT URINES IN CASES IN WHICH THERE WAS NOCTURNAL POLYURIA (MORE THAN 750 C.C.) ON EITHER A HIGH OR LOW PROTEIN DIET. IN EVERY INSTANCE A GREATER AMOUNT OF SOLIDS IS ELIMINATED WITH THE LARGER VOLUME OF NIGHT URINE, THUS INDICATING THAT IT IS THE NECESSITY OF EXCRETION OF SOLIDS THAT CAUSES A NYCTURIA

Diagnosis	Phenol-sulphone-phthalein, Per Cent	Night Urine					
		Low Diet			High Diet		
		Volume, c.c.	NaCl Gm.	N Gm.	Volume, c.c.	NaCl Gm.	N Gm.
Chronic nephritis.....	0	720	2.02	3.67	*840*	2.86	4.12
Chronic nephritis.....	10	475	1.62	2.09	*1055*	4.01	3.69
Chronic nephritis.....	16	590	2.12	2.42	*925*	3.52	2.87
Chronic nephritis.....	20	535	2.68	2.14	*1147*	6.07	6.07
Chronic nephritis.....	31	740	4.22	4.00	*790*	4.66	4.19
Chronic nephritis.....	32	400	1.28	3.20	*780*	3.20	5.30
Chronic nephritis.....	37	610	4.03	2.68	*1300*	8.32	4.29
Chronic nephritis.....	39	470	2.44	1.44	*820*	5.58	4.02
Chronic nephritis.....	39	*1000*	5.40	3.50	335	2.61	3.47
Chronic nephritis.....	45	595	1.79	2.92	*1910*	4.39	5.73
Chronic nephritis.....	46	525	1.10	4.52	*1170*	2.46	4.68
Essential hypertension..	63	415	4.07	4.57	*900*	9.18	7.11
Essential hypertension..	60	*1040*	4.68	2.70	550	3.58	4.02
Essential hypertension..	57	565	4.80	2.88	*767*	5.52	4.60
Essential hypertension..	59	725	4.35	2.32	*1240*	9.18	5.08
Acute nephritis.....	24	440	1.36	2.68	*860*	3.27	5.07
Acute nephritis.....	35	740	3.26	2.59	*1160*	4.64	4.18
Acute nephritis.....	61	660	1.65	3.17	*795*	1.91	3.98
Pyelitis and cystitis....	65	415	1.83	2.78	*780*	3.98	3.59
Anemia	..	520	2.81	1.82	*1250*	2.75	6.34
Chronic arthritis.....	75	507	2.26	2.86	*1004*	5.75	4.66

night urine occurred only in the specimen corresponding to the high diet and only two in whom the opposite held true. However, the amount of salt and nitrogen eliminated was greater with the large quantity of night urine, indicating that the necessity of the excretion of a large amount of solids by a dilute urine was the controlling factor in every instance. It is thus seen that in many instances a suitable diet may do away with a nocturnal polyuria and relieve the kidney from some of the strain which it would otherwise be subjected to.

Nycturia as well as a polyuria during the whole twenty-four hour period has been correctly regarded as a phenomenon which compensates to a certain degree for the inability of the kidney to eliminate solids by concentration in the urine. Foster(*a*)(1916) has demonstrated how an increased output of water in the nephritic patient serves to carry an increased amount of nitrogenous material with it. In Bright's disease, however, there is another factor to consider and this is that a polyuria, implying as it does an abnormal effort on the kidney, may finally result in renal fatigue and a diminished urinary output. Schlayer originally substantiated this fact. The author has seen an oliguria occur after glucose infusions and the ingestion of inordinately large amounts of water, both of which procedures were supposed to result in exactly the opposite effect.

In the management of these problems it must be remembered that a minimal level of protein metabolism is achieved by a diet high in starches and low in protein, and not by starvation. When no food whatsoever is taken the kidneys must eliminate about eight grams of nitrogen a day, while if the starches are forced, the amount excreted may be diminished by half, thus sparing the kidney a great deal.

The *elimination of salt and nitrogen* furnish some, though a limited amount of information, as to renal function. If the concentration of salt or nitrogen is one per cent or higher and that of urea twice as great, in any specimen obtained, the power to concentrate these substances may be considered to be normal, the total output then depends upon the ability of the kidney to excrete water. The elimination of any solid material in the urine is controlled by these two factors, degree of concentration and volume of fluid elimination, and must be judged accordingly.

The fact that the sodium chlorid concentration may be much diminished while that of the nitrogen or urea remains high has already been alluded to. (Table 30.) This relation is especially characteristic of myocardial insufficiency and acute or chronic nephritis associated with edema. In general it has been observed time and again, that the power of the kidney to excrete salt is curtailed before the ability to eliminate nitrogenous substances is involved to the same extent.

The total quantities of salt, urea or nitrogen put out in 24 hours and

the balance of these figures with the intake has a very limited application. This has been taken up under nitrogen balance. If such studies are desired it is necessary to measure the quantities ingested and much labor is added to carrying out the test day for renal function. If the patient's routine dietary is followed during this procedure a distinct amount of information can be gained as to the adequacy of the food in any given case. An example of such an interpretation is given in Table 28, in which it is shown that the subject is drinking too little water and eating too small an amount of proteins to maintain life. An instance of overindulgence in food is given in Table 33.

TABLE 33

TEST DAY FOR RENAL FUNCTION WHILE THE PATIENT IS TAKING HIS CUSTOMARY DIET. THE FLUID INTAKE IS TOO LOW (HIGH FIXED SPECIFIC GRAVITY); THE AMOUNT OF STARCHES AND PROTEINS EATEN ARE EXCESSIVE (HIGH BLOOD SUGAR, LARGE UREA OUTPUT)

Time	Vol. c.c.	Sp. Gr.	NaCl %	NaCl gm.	Urea %	Urea gm.
8-10	45	1025				
10-12	100	25				
12- 2	140	21				
2- 4	165	22				
4- 6	128	25				
6-10	205	25				
Total day	783	....	1.10	8.61	2.3	18.0
10-8	475	1026	.96	4.56	2.7	13.0
Total	1258	....	...	13.17	...	31.0

P. J. Age 56, Blood Pressure 146/48, Weight 215 lbs.

Blood Sugar .16 per cent; Urea N 11.9 mg., Uric Acid 2.8 mg., and creatinin 2.9 mg. per 100 c.c.

Urine No albumin. no sugar, microscopic examination negative.

Diagnosis Obesity.

Renal Function Normal.

Metabolism Too little fluid, excessive starch and protein intake.

In judging of the improper metabolism of patients while the test day for renal function is carried out the chemical blood determinations are indispensable as may be gathered from Tables 28 and 33. By these means it may be determined whether a low output is due to insufficient kidney action or to a faulty diet. The carbohydrate metabolism may also be investigated in this way to a limited extent as shown in Table 33.

A summary of the criteria of value and their interpretation when the test day for renal function is carried out while the patient is taking his routine diet, is as follows: (Mosenthal(*e*), 1920).

Criterion	*Normal Standard.*	*Significance.*
Maximal specific gravity.	1920 +	Ability of the kidney to concentrate the urine. If this is as high or higher than the normal standard, renal excretion is satisfactory provided the amount of urine is adequate. This may be regarded as a definite criterion of renal function which is independent of the diet administered. Long life is often possible even if the specific gravity is below normal, provided the inability of the kidney to concentrate is compensated by polyuria, as in diabetes insipidus and a few cases of chronic nephritis.
Fixation specific gravity.	Variation of 9 degrees	Normal renal activity is characterized by variation of the specific gravity in the urinary specimens. (a) A high fixed specific gravity may occur in normal individuals because they take too little fluid to meet their bodily needs. The possibility of determining this makes the two-hour test especially valuable in ambulant patients who are taking their usual amount of food and fluid and are pursuing their accustomed occupations. (b) A high fixed specific gravity may be brought about by diseases characterized by edema and oliguria, especially myocardial insufficiency and acute or chronic nephritis. (c) A low fixed specific gravity is found in many widely varying conditions: diabetes insipidus, chronic nephritis, marked anemia, the elimination of edema, cystitis, pyelitis, polycystic kidney, prostatic hypertrophy, urethral stricture, paralysis of the bladder (as in tabes dorsalis or tumor of the cord), etc. Such patients do well as long as polyuria com-

Criterion	*Normal Standard.*	*Significance.*
		pensates for the lack of power to concentrate.
Nocturnal polyuria	usually 400 c.c. or less. In some individuals as high as 750 c.c.	A high night urine means that the kidney is putting forth a greater effort than it normally should. This overstrain may cause fatigue, that is, functional damage, if continued indefinitely. In nephritis, the increased night urine may be reduced by curtailing the salt and protein intake. By testing the ambulant patient while on his normal diet we are in a position to judge as to the effect the customary food and habits have upon the volume of night urine and to advise the patient intelligently as to the modification of the diet. The chemical examinations of the urine and blood tell us in what respects the food intake should be changed.
Sodium chlorid excretion.		This is being taken in greater amounts than necessary if more than 5 grams are present in the twenty-four hour urinary specimen. The amount in the food should be reduced if therapeutic indications demand it. If the amount in the urine is very low and edema exists, then the elimination of salt is insufficient and the amount in the urine cannot be regarded as an index of the quantity in the food.
Nitrogen excretion		If 5 or 6 grams are eliminated in the urine (or double the amount of urea), there is sufficient protein in the food to maintain an individual's health and strength, provided the diet contains a considerable amount of starch. Unless the disease is of such a nature as to demand the restriction of protein food it is not necessary to limit the protein ration.

Criterion	*Normal Standard.*	*Significance.*
		The blood uric acid, urea, and creatinin indicate whether there has been any retention of these products. These findings must be taken into consideration with the urinary analyses in order to come to a definite conclusion regarding the kind and amount of protein food that is best for the patient in question.
Sodium chlorid concentration.		Normal if one per cent or higher in any specimen of urine; not necessarily abnormal if less.
Nitrogen concentration		Normal if one per cent or higher in any specimen of urine; not necessarily abnormal if less.
Urea concentration		Normal if two per cent or higher in any specimen; not necessarily abnormal if less.
Low sodium chlorid and high urea or nitrogen concentration.		Characteristic of myocardial insufficiency and nephritis accompanied by edema.

Concentration and Dilution Test

Volhard originated a procedure which has been called the concentration and dilution test. Kövesi and Roth Schulz had previously tested the power of the kidneys to excrete a dilute urine by giving large quantities of water and combined this with cryoscopic examination of the urine to determine the molecular concentration. Various authors have advocated similar tests until Volhard's technique has finally superseded the others; this is as follows: the urine is voided at 7.30 A.M and is discarded; between 7.30 and 8 A.M. 1500 c.c. of fluid are taken (this may be milk, coffee diluted with milk, weak tea, peppermint water; the main point is that the fluid should be mostly water; 1 to 2 rolls may be given with the fluid); the urine is voided at the intervals given in Table 34; the volume of each specimen is measured and its specific gravity noted; the method as outlined thus far, aims at ascertaining the ability of the kidney to dilute, in order to test out its power of concentration, solid food, but no fluid is added in the course of the day somewhat according to the following schedule:

8 A.M. Roll 80 gm., butter 20 gm., marmalade.
10 A.M. Roll 80 gm., butter 15 gm., 1 egg
12 Noon Meat 100 gm., mashed potato or rice 200 gm., vegetable 100 gm., fruit, fresh or stewed 100 gm.
4 P.M. Roll 80 gm., butter 20 gm., marmalade 40 gm.
7 P.M. Roll 80 to 120 gm., butter 10-20 gm., meat 50-100 gm., 2 eggs.

In normal individuals the fluid ingested is largely excreted within two hours; subsequently the concentration of the urine rises. Examples of this method of testing renal function are given in Table 34 taken from Munk's book.

TABLE 34

EXAMPLES OF COMBINED DILUTION AND CONCENTRATION TESTS AS GIVEN BY MUNK

Normal Individual				*Chronic Nephritis*			
Time	Urine		Fluid Intake, c.c.	Time	Urine		Fluid Intake, c.c.
	Volume, c.c.	Specific Gravity			Volume, c.c.	Specific Gravity	
7.30 A.M.			1500	7.30 A.M.			1500
8.00 A.M.	135	1029		8.00 A.M.	185	1009	
8.30 A.M.	100	1013		8.30 A.M.	295	1005	
9.00 A.M.	400	1003		9.00 A.M.	225	1004	
9.30 A.M.	520	1002		9.30 A.M.	260	1003	
10.00 A.M.	285	1004		10.00 A.M.	190	1005	
11.00 A.M.	55	1015		11.00 A.M.	215	1006	
12.00 M.	80	1017		12.00 M.	155	1005	
2.00 P.M.	65	1025		2.00 P.M.	105	1012	
4.00 P.M.	95	1028		4.00 P.M.	170	1016	
6.00 P.M.	110	1023		6.00 P.M.	125	1013	
8.00 P.M.	50	1027		8.00 P.M.	202	1013	
8.00 A.M.	210	1031		8.00 A.M.	335	1016	

This method yields results that are as satisfactory, but not more so than the test day for renal function. However, it entails too much discomfort for the patient ever to become a method of choice. The same criteria in regard to nocturnal polyuria, fixation of specific gravity, etc., as given under the caption of test day for renal function, apply here. The method has been given in detail because it evidently is used extensively in German clinics and may come to be employed in this country.

Uremia

Introduction and Definition

Uremia, as the term implies, was originally conceived to be a condition in which urea accumulated in the blood and tissues as the result of inadequate kidney activity. At that time the whole problem of nephritis was

regarded as one depending solely upon the amount of fluid and solids excreted in the urine. It was supposed that if there was retention of waste products a certain series of symptoms ensued, on the other hand, if the urine was sufficient nothing was to be apprehended. The clinical observations of the last few years, especially the results obtained by numberless blood chemical determinations, have given this long entrenched conservative theory a rude shock. Through these efforts it has developed that the so-called uremic complex may occur whether the urea—and many other constituents of the blood—are increased or normal. The name uremia, however, remains even if the facts which it implies have been proved to be incorrect.

This retention of a term that has long outlived its significance is most confusing. The term uremia ought to be confined to that state in which the blood urea is distinctly increased. Renal insufficiency followed by the accumulation of waste products in the blood entails a fairly definite symptom complex that may be grouped as uremia. Even if the meaning of the word is thus limited, it is doubtful whether uremia should be retained as a term, since it is certain at the present time that the blood urea is only one of a considerable number of substances that the kidney fails to eliminate. It would be much better to speak of the rather well defined syndrome accompanying marked oliguria or anuria, which will be described subsequently, not as uremia but by a name which actually states the facts as they are, such as kidney insufficiency.

If the term kidney insufficiency is used to cover part of the meaning usually conveyed by the word uremia. how shall the remainder be designated? A curious contradiction has arisen as time has passed by. By some authors and clinicians, those toxic states, accompanying Bright's disease, characterized by convulsions and other signs of irritation of the nervous system have been called uremia. whereas those in which drowsiness and somnolence have predominated have not been put in this category. Yet it is the latter state in which the blood urea is usually high; and it is the former condition in which only a comparatively slight increase in the blood urea and frequently none at all occurs that has had the name of uremia attached to it. Such toxic symptoms accompanying Bright's disease without renal insufficiency are very variable and their clinical picture can not be adequately summarized by one word. It would avoid confusion if these manifestations were described as nephritic headache, nephritic convulsions, nephritic vomiting, etc., whenever the diagnostician believed them to be secondary to the diseased process in the kidney. Janeway in a similar way some years ago successfully designated a certain form of headache as hypertensive headache.

Ascoli has given the most satisfactory definition of uremia. It is a succinct statement of fact and does not attempt to evade the issue that there is no clear cut conception of what the uremic state really is. His

statement is somewhat as follows: Uremia is any toxic state or symptom associated with a renal lesion; it is tempting and justifiable to add, provided no other cause can be found to account for the toxic state or symptom. Since Ascoli's time one large group of cases has been taken out of the category of uremia. The recent intensive study of renal function, coupled with pathological observations, has made it clear that cerebral arteriosclerosis and its attendant changes are responsible for many instances formerly considered to be uremia. These facts will be taken up in greater detail a little further on, but this may serve as an example of how the term uremia will gradually be more and more limited until it obtains a definite significance which it does not possess at present. The writer wishes to call attention again to the point brought out in the first paragraphs of this section, namely, that the term uremia has outlived its day and that those conditions brought on by inadequate kidney function should be grouped as renal insufficiency, and those states occurring in the course of Bright's disease, but not accompanied by deficient kidney activity, should be designated as nephritic convulsions, nephritic vomiting, etc., thus at least making the clinical diagnosis perfectly clear.

Uremia, as Described by Julius Cohnheim in 1882

It is remarkable how little progress has been made during many years in determining the etiology of uremia. A good idea of the lack of advance in this direction may be obtained by reading what Julius Cohnheim (*a*) wrote about this subject in 1882; his presentation is interesting, stimulating, and does not differ very markedly in many respects from the exposition given by other authors since that time; it forms a very good starting point from which to note what meager changes in the conception of uremia have come about in a period of almost forty years and will give the reader a much clearer idea and broader view of the question of uremia than if only the latest efforts on the subject, which are largely a repetition of the older ones, are discussed. Cohnheim's exposition given partly in summary and partly as a literal translation is as follows:

By the term uremia is meant a series of nervous symptoms which may develop suddenly or slowly, that is, may be acute or chronic. In the acute form unconsciousness or epileptiform convulsions are followed by deep coma; prodromal symptoms, especially severe headache, or vomiting may be present; during the coma there may be a few or numerous clonic convulsions. These attacks may be repeated several times and apparently complete recovery take place in the interval, until at last, the comatose state terminates in death. In the chronic form the course is less stormy; at first, irritability, somnolence and apathy develop; slowly but surely these symptoms increase and a constantly deepening coma supervenes which has an invariably fatal issue.

Even though these disturbances occur in the course of a nephritis it can not be accepted as proved that they depend upon the renal disease and it is also perfectly evident that the pathologicophysiological process at fault is not explained. Uremic manifestations occur in all sort of renal conditions. However, it appears that the majority of instances of uremia accompany kidney disease in which there is a diminished excretion of water and of solid substances. Acute nephritis, chronic nephritis, bilateral obstruction of the ureters, impermeable urethral strictures, eclampsia, cholera and, in fact, all conditions in which the urinary secretion is very much diminished, or lacking entirely, fall in this category.

Animals in which anuria is effected in various ways, by ligature of the renal arteries or of the ureters, or by double nephrectomy, succumb in a few days. Vomiting, diarrhea, apathy, somnolence, coma and death are the main symptoms. Convulsive seizures do not occur.

Voit(*d*) showed that urea accumulated in the blood and tissues of such animals. It is tempting to assume that this is the causative agent responsible for the poisoning. Injection experiments, however, prove that this is not the case. Neither the venous infusion of urine nor solutions of urea apparently produced any pathological manifestations (consult Frerichs (*b*)). Furthermore, it was found that the blood urea is not necessarily high when uremia occurs. Frerichs elaborated the idea of the toxicity of urea by attributing the uremic symptoms to ammonium carbamate which he believed to be derived from urea through the action of a ferment. At present, however, it is established that neither this substance nor ammonia occurs in the body under normal circumstances or when uremia exists and Frerichs' brilliant idea must therefore be dropped.

Chemical theories evidently have not been adequate to account for uremia; other efforts in this direction have not been any more successful, but some of them will be mentioned. A number of authors, who were especially anxious to account for the nervous manifestations of uremia, have attached much importance to inflammatory changes of the cerebral meninges (Osborne), and to congestion of the brain, and finally Traube proposed a theory which was well thought out in certain directions and rather vague in others. He proposed to explain the occurrence of coma by edema of the midbrain; the edema was supposed to depend on two factors, the increased arterial pressure and the disturbed osmotic relations entailed by the diminished protein content of the blood. All experimental evidence, even after enormous infusions of saline solution, fails to confirm either contention; neither an increased blood pressure nor a marked hydremia will bring about cerebral edema. It is not necessary to discuss this theory in greater detail because cerebral edema is not constantly present in uremic subjects. I can assure you, that in the two decades that have passed since Traube published his ideas, I have examined many brains of those dying with uremia, and found them to be normal in every way.

Therefore we are justified in assuming that cerebral edema may be an accidental accompaniment of the uremic state, but that it cannot be its cause.

The venous infusion of urine, or urinary constituents, such as urea, will not result in any untoward symptoms unless the excretion of such substances by the kidney is checked. If the infusion is preceded by ligation of the ureters, vomiting, diarrhea, etc., develop much more rapidly than if the latter operation had been the sole procedure and the venous injection had no tbeen resorted to. This demonstrates that the urinary waste products have a distinct bearing upon the problem of uremia. Voit has furnished proof for this contention by a very striking experiment. A small dog, weighing 3 kg., was given 18 gm. of urea; the animal was allowed to drink as much water as it chose, and within 24 hours the urea was eliminated without difficulty; the effective excretion was accomplished largely by polyuria. If the experiment was conducted as before, except that the water intake was restricted, an entirely different picture developed: a few hours after the administration of the urea, there was evident prostration, and shortly afterwards violent attacks of vomiting came on, which were repeated on this as well as the following day; in the meantime, the dog became progressively weaker and more apathetic, there were marked muscular twitchings and cramps, and the animal was evidently in a very precarious state. All these symptoms were, however, set aside when water was again administered and polyuria established. From these observations it is possible to conclude that large amounts of urea may readily pass through the body without detrimental effect, although the accumulation of urea in the blood and tissues, because of insufficient kidney action, is fraught with dire consequences. On the other hand, not all investigators obtained similar results. Thus, after injection experiments, Astaschewsky denied that either urea or creatinin had any toxic effect; he believed the mineral salts, especially potassium, to be of much more importance. Since the cause of uremia can not be recognized in any single substance it becomes evident that from the practical point of view it will be preferable not to consider uremia to be brought about by this or that substance, but by a retention of all the solid constituents ordinarily contained in the urine. The particular cause of the renal insufficiency is of little moment in this connection. A variety of conditions, very unlike each other from the clinical, anatomical or pathologicophysiological point of view, may be responsible for the oliguria or anuria. Thus the inspissation of the blood entailed by cholera or any marked diarrheic state, eclamptic seizures, acute or chronic nephritis, mechanical obstruction of both ureters or the urethra may diminish the urinary output. The same effect is produced (Bartels (*d*)) in some cases of edematous nephritis when there is a rapid elimination of fluid. Presumably under these circumstances the solids are not eliminated with equal speed, and an inspissation of the blood, the possible cause of uremic symptoms, results.

It has been suggested by no less an authority than Rosenstein, that uremia must have a multiple etiology because of the diversity of its symptoms. This does not agree with the explanation of urinary insufficiency as the sole cause, offered in the preceding paragraph. (Cohnheim then goes on at length to show how the various forms of uremia are all due to retention of products ordinarily excreted by the kidney; inasmuch as we now know from studies in blood chemistry that this is not so, this part of Cohnheim's discussion is omitted. The subject will be taken up in greater detail, and from the more recent viewpoint, in the next section.)

More Recent Aspects of Uremia

Cohnheim attempted to ascribe all the conditions that had been described as uremia to one factor,—renal insufficiency. The reasoning was excellent as far as it could go at that time, and was correct from the point of view that every instance of renal insufficiency may result in uremia; but the converse, that every case of uremia is due to inadequate kidney function is not true. What is to-day frequently considered to be uremia may be divided into three groups, as already outlined in the introduction.

1. Those conditions whose symptomatology resembles that of uremia, but whose occurrence is not dependent upon nor necessarily associated with diseases of the kidney.

2. The symptom complex depending upon renal insufficiency, which has also been called retention uremia (Foster(*a*), 1916).

3. The clinical picture whose manifestations apparently depend principally upon an irritation of the central nervous system; it accompanies the various forms of Bright's disease but is not dependent upon renal insufficiency.

Conditions Hitherto Often Erroneously Classified as Uremia.—It is now recognized, largely through the efforts of Sir Clifford Allbutt(*a*), that increased arterial pressure is not necessarily dependent upon renal disorders but is in many instances an independent disease. (See section on blood pressure.) This condition, which has been most commonly known as essential hypertension, entails, among other changes, arteriosclerotic lesions in the cerebral blood vessels. These in turn can produce areas of softening and hemorrhages in the brain tissue. Vomiting, palsies, temporary or permanent, convulsions, coma, etc., are often due to such anatomical changes and not to some mysteriously elaborated poison. There had been only one alternative offered as an explanation of these manifestations, and that is that temporary anemia brought on by arterial spasm may be responsible. Osler and Pal have been particularly enthusiastic in advocating this possibility.

The diagnosis of this condition is not difficult. If the symptoms of irritation or depression of the central nervous system are present, a distinctly elevated blood pressure exists, and the tests for renal function indicate little or no curtailment of kidney efficiency, then it is justifiable to assume that a cerebral arteriosclerosis is responsible for the symptoms. The inability of clinicians to carry out tests for renal function in the past few years has led to the inclusion of many of these cases among those reported, described and discussed as uremia. For instance, Ascolis' famous book on uremia evidently has many such instances in it.

One of the very interesting and important aspects of this later explanation of uremia is whether all the bizarre palsies of a fleeting or permanent character that may affect many muscles, or only one limb or even a single muscle, are not due to cerebral arteriosclerosis, and whether it is necessary to invoke the aid of toxins of any sort to explain them. It is unnecessary to add any further evidence to that already furnished by Cohnheim (see preceding section) to deny that cerebral edema can have any bearing. The whole matter can be cleared up only by careful clinical observation followed by thorough and painstaking anatomical studies. Such authorities as Krehl and Munk admit that grievous errors have been made in confusing cerebral arteriosclerosis and uremia. The author is of the opinion that, as time passes by, the focal lesions of the central nervous system attributed to "uremic poisoning" will in large part be traced back to pathological changes in the cerebral arteries, occurring as an affection entirely independent of Bright's disease.

Renal Insufficiency.—The poisoning characteristic of renal insufficiency has been elucidated in several particulars during the past few years. Intensive studies in blood chemistry by innumerable workers in many institutions have made some of these conclusions possible. In the first place, it is necessary to have the symptoms produced by marked renal insufficiency clearly in mind.

Foster(*c*)(1921) describes this condition very well: "I studied with the greatest care from day to day, three patients who had been deprived of the only functioning kidney by emergency operations. In none of these was there the slightest evidence of irritability of the motor nervous system, or impairment of the psychic functions until the last days of life. None had amaurosis, muscle spasms, paralysis or convulsions. All alike experienced first, weakness, slight vertigo and mental dullness; then a tendency to sleep which lapsed into coma, with death on the ninth to eleventh day after the operation." The author agrees with these findings except in one particular: when the kidney becomes absolutely insufficient, or nearly so, and the waste products accumulate within the body, an almost constant symptom is rather fine muscular twitchings, noted in any of the voluntary muscles and especially the forearms, hands and fingers; this muscular twitching will frequently precede the onset of coma for several days

and when coma has supervened may point to the true cause of the unconsciousness making a differential diagnosis (for instance from the coma accompanying cerebral hemorrhage) possible. Furthermore, it should be mentioned (see section on hypertension) that in some of these cases there is a slight rise in blood pressure. Janeway reported a systolic pressure of 180 mm. of mercury in a man whose only kidney had been removed; various observers have noted an increase in arterial pressure accompanying anuria or marked oliguria from any cause whatsoever, though it is not a constant symptom. In one recent case of ureteral obstruction due to carcinomatous involvement of the bladder and ureters, the systolic blood pressure was 130 mm. of mercury.

"With Blum we may distinguish uremia, i. e., the effects due to toxic products of metabolism before their passage through the kidney, and urotoxemia, the absorption of urinary toxic bodies after their passage through the kidney. Now any condition of urinary obstruction must be a compound of these two forms of intoxication" (Golla). Much time and effort has been spent in elucidating the above fascinating theory. So far no proof has been brought that the toxicity of retained materials due to urethral obstruction is different from that brought on by double nephrectomy. The final demonstration of this fact was brought by the ureterovenous anastomoses performed by Reid upon dogs. The writer carried out double nephrectomy in other animals in the same laboratory and noted that the dogs without kidneys, and those excreting their urine into their own veins, died with the same symptoms, after the same interval, and gave no evidences of significant differences in their blood chemistry. It may therefore be concluded that the kidney does not intensify the toxicity of the waste products it excretes. Why this should ever have been supposed to be so is another matter.

Innumerable animal experiments in which the ureters or renal vessels have been tied, the kidneys partially or completely extirpated or ureterovenous anastomoses performed (Reid) have failed to produce the much desired convulsive form of uremia. The animals have invariably become drowsy, then comatose and finally died. The human symptoms and those in animals have proved to be identical. These results have made it perfectly clear that anuria or markedly insufficient kidney action brings about a definite clinical picture; whether a single substance, of the many renal excretory products retained, is responsible for this state, or whether all of them combined bring it about, remains to be determined. It is only natural that the search has been directed towards a single chemical factor that may be responsible for this form of uremic coma.

Urea has been the substance most frequently considered to be the cause of uremia, ever since Babington in 1836 found this material to be increased in the blood during renal insufficiency. Since that time Frerichs advanced his brilliant but untenable theory that the toxic material was

not urea but ammonium carbamate derived from the urea. This has already been taken up in the previous section. The most recent investigations in regard to the effect of urea are those of Hewlett, Gilbert and Wickett, who found that the ingestion of large amounts of urea (raising the blood urea nitrogen as high as 111.4 mg. of urea nitrogen per 100 c.c.) produces a certain train of symptoms comparable to those encountered with marked renal insufficiency (asthenic type of uremia): headache, dizziness, apathy, drowsiness, bodily weakness, and fatigue. Such symptoms appeared when the blood urea nitrogen rose above 68.2 per 100 c.c., and disappeared when it fell below this level. These observations would indicate that certain toxic phenomena could be ascribed to an accumulation of urea in the blood. On the other hand, it is a common experience to find blood urea values as given above, and even higher, while the patient complains of no symptoms whatsoever. The writer has followed one such case for almost two years and there are many other similar ones on record. It is probable that the sudden flooding of the body with a substance, such as urea, for the time being disturbs the existing osmotic relations, but if the material accumulates more slowly, compensatory adjustments are made that forestall the appearance of symptoms. That urea in itself, except in huge amounts, should be responsible for the manifestations of renal insufficiency, is therefore improbable.

Creatinin has been considered as a possible causative agent of the uremia brought on by renal insufficiency. What has been stated regarding this substance under the heading of creatinin in nephritis may be repeated here. It is probable that creatinin in itself has little or no toxic effect. This is demonstrated by the absence of untoward symptoms in the numerous experiments on man and animals in which creatinin has been injected or ingested. Myers and Killian(*b*) believe that it may be the cause of uremia. This, however, is based only upon theoretical grounds and is contradicted by the evidence cited in the same paper that some cases, with a high blood creatinin, survive a considerable length of time. A rise in the blood creatinin certainly must be looked upon as a grave sign of renal insufficiency. The kidney eliminates creatinin with great ease, and this substance is therefore among the last of the end products of protein metabolism to be increased in the blood (see section on relation of uric acid, urea and creatinin in the blood in nephritis). An augmentation of creatinin in the blood is, however, only a signal of marked renal insufficiency; in itself it has no further significance. The actual cause of uremia, brought on by retention of waste products, can not be attributed to creatinin but is to be sought in other substances which are simultaneously held back by the damaged kidney.

Creatin has been suggested at various times as a cause of uremia. As stated under the heading of Creatin in Nephritis, it is probable that creatin in increased amounts in the blood and to a lesser extent in the tissues,

is the result of accelerated protein disintegration characteristic of the terminal stages of Bright's disease, and in itself is a symptom rather than a cause of any toxic state.

Uric acid has here and there been referred to as a possible causative agent for toxic symptoms in renal insufficiency. The fact that in both gout and leukemia the uric acid may reach higher levels in the blood than it will in nephritis, is sufficient evidence of the incorrectness of this view.

An old idea that *potassium* when retained because of renal insufficiency may cause toxic symptoms has recently been revived by Smillie(*a*). Observations on man and animals were offered to support this contention. Macallum found the potassium in the blood raised in a few cases of nephritis. Recently Myers and Short again took up this problem and conclude that: "The few observations reported on cases of nephritis with marked nitrogen retention do not appear to support the suggestion that possibly some of the symptoms of uremia are due to a potassium poisoning, as a result of the retention of this element." Thus the recent reassertion of the importance of potassium as a toxic substance in renal insufficiency has met the same denial that was accorded it many years ago.

Sodium Chlorid, curiously enough, has not been credited with producing the asthenic symptoms characteristic of renal insufficiency, but rather with those found in the convulsive type of poisoning accompanying Bright's disease. It will be taken up in greater detail in the next section on nephritic toxicosis.

Indicanemia has been proposed as a cause of intoxication following upon renal insufficiency by Obermayer and Popper. Here, as with all substances that are retained because of deficient kidney action, the mere occurrence of the substance in the blood does not furnish conclusive evidence that it is the agent above all others that is responsible for "uremic" manifestations.

One of the few factors which has come to play a more or less definite rôle in the poisoning brought on by renal insufficiency is *acidosis.* Sellards(*b*), Straub and Schlayer, Peabody(*c*)(*e*), Palmer(*a*)(*d*), Chace and Myers(*c*), and many others have pointed out that this phenomenon is prone to exist when the retention of urinary excretory products becomes acute. Peabody in 1915 came to the following conclusions in regard to the acidosis accompanying nephritis:

1. In mild cases of chronic nephritis, in which renal function approaches the normal, there is usually little or no acidosis.
2. More advanced cases show an acidosis by the "alkali tolerance" test (Sellards) but there may be no fall in the alveolar carbon dioxid tension.

3. Only in very advanced cases is the acidosis usually so marked as to cause a decrease in the alveolar carbon dioxid tension. This is not true in all instances.
4. The acidosis of chronic nephritis is due to a retention resulting from inefficient renal excretion.

It has been detailed under the heading of phosphates in nephritis, how the retention of acid phosphates is responsible for the nephritic acidosis. Chace and Myers have come to the conclusion that all fatal cases of chronic nephritis with marked nitrogen retention show a severe acidosis sufficient in many instances to be the actual cause of death; the same seemed to hold true for some of the patients suffering with acute nephritis. They found that alkali therapy by mouth and infusion causes the symptoms to disappear.

Advanced bilateral cystic degeneration of the kidneys offers the clinician a rare opportunity of studying kidney insufficiency in its purest form. In chronic or acute nephritis there usually are degenerative, inflammatory or arteriosclerotic changes in tissues outside of the kidney, and functional anomalies such as hypertension, myocardial insufficiency, etc.; any symptom or sign regarded as due to lowered efficiency of the kidney in nephritis consequently demands close scrutiny. The case of bilateral cystic kidneys reported by Means and Roger is therefore of extreme interest (in this patient there was no increased blood pressure such as is often present in this malady). These authors found that the death of a colored man, 46 years old, was apparently caused by acidosis of very marked degree (the carbon dioxid tension in the alveolar air going as low as 6.4 mm. of mercury and the carbon dioxid capacity of the plasma —determined according to Van Slyke—dropping to 12 volumes per cent). The author has seen a similar case in which the acidosis, while not so severe, was very marked. This patient, during the course of a year and a half, was saved from what appeared to be impending "uremic coma" on three occasions by the administration of alkali.

From what has been said it becomes perfectly evident that in many cases which die as the result of diminished kidney activity, acidosis is the determining factor which brings about the fatal outcome. The writer has believed this to be true for some years and after observing a good many cases has finally come to the conclusion that the above idea is correct in the majority of cases but is not a universal rule. Recently, a case of secondary contracted kidney, that had been watched carefully for several weeks, died the slow death characteristic of markedly impaired renal function, while the carbon dioxid combining power of the blood was 45 volumes per cent. There were many petechial spots (blood cultures negative and no definite proof of terminal infection) and evidently another immediate cause of death than acidosis would have to be sought in this case. The

exception may not prove the rule, but it is very probable that Chace and Myers are correct in supposing that the determining factor in bringing about death from renal insufficiency in many instances is an acidosis attendant upon the inability of the kidney to excrete acid phosphates.

A *disturbed water metabolism* may be a distinct contributing factor towards producing renal insufficiency. This may be brought about in a number of ways. It has been previously mentioned that the sudden excretion of large volumes of fluid in edematous patients may bring about a harmful degree of blood and tissue concentration. Foster and Davis have shown that in the severer cases of nephritis in which the power to concentrate solids in the urine is much diminished there is a considerable increase in non-protein nitrogenous constituents of the blood where the water intake was curtailed. Mosenthal(*a*) had demonstrated in experimental nephritis in dogs that a part at least of the increase of non-protein nitrogen in the blood must be attributed to inspissation; the kidney, with its polyuric tendency, in these conditions acts like a suction cup that drains the body of every available drop of water. That the signs of renal insufficiency may be marked if there is not enough water available to form urine is possibly best illustrated by the constantly quoted fact that in cholera, when the intestines deplete the body of fluid, anuria results even though the kidneys are anatomically intact.

It is a well known fact that animals deprived of water will not live as long while starving as those that are allowed to drink (Nothwang, Landauer). Desiccation will hasten a fatal outcome, as any one who has seen many cases of diabetes mellitus and nephritis must appreciate. It is almost a clinical proverb, not without its exceptions to be sure, that a diabetic patient will not die if he exhibits some sign of edema. Besides the above well founded bedside impression, there is one fact that has been experimentally established, on both man and animals, which must have a bearing in this connection: there is a distinct increase in protein catabolism when the fluid intake is excessively curtailed (Denning, Landauer, Straub(*b*)).

It may be readily gathered, from all the factors mentioned above, which may be ascribed to an inadequate water drinking: increased tissue and blood concentration, diminished excretion of urine, and an acceleration of protein catabolism, that water deprivation may in many instances be a distinct contributing factor, and at times the main cause for the occurrence of the symptoms of a marked renal insufficiency.

Protein destruction as a possible cause of the intoxication following renal insufficiency has already been discussed under the heading of "protein destruction in nephritis." The conclusion arrived at was that this phenomenon was a state accompanying renal insufficiency of a very marked degree, being a symptom, but not a causative factor of the "uremic poisoning."

Nephritic Toxicosis

There is a form of poisoning accompanying nephritis whose main characteristic is found in signs and symptoms brought on by an irritation of the central nervous system. This has been variously called sthenic uremia, convulsive uremia, epileptiform uremia, eclamptic uremia, etc. The appellation uremia is absolutely incorrect inasmuch as this symptom complex is not necessarily accompanied by an increase in the amount of of urea in the blood. It is invariably associated with Bright's disease in the minds of all. However, it must be acknowledged that similar clinical pictures occur, for instance, in cerebrospinal meningitis. Under the circumstances there is a peculiar state of affairs that confronts the physician: a symptom complex whose most prominent feature is convulsive phenomena, has no definite cause; since nephritis often accompanies it, it has been termed uremia. It is not at all certain that this condition, sthenic uremia, is a sequel to changes in the kidney; it is extremely important to bear this fact in mind. It is much more probable that the same unknown poison is responsible for both the nephritis and the nervous manifestations. There are a number of cases in which the convulsive seizures have occurred previous to any signs of renal disease, which sequence could only be explained on the supposition just expressed, that the same toxic material is the cause for either change and one is in no way dependent on the other. The term *nephritic toxicosis* is much more expressive of what is really meant by this condition; uremia as just explained is an utter misnomer; if the individual symptoms of this state are to be described it would be best to designate them by the term nephritic, as nephritic convulsions, headache, etc. This has already been discussed under the heading of introduction and definition in this section on uremia.

The greatest progress in clearing up the situation has been made in the so-called toxemias of pregnancy. Even here the advance has not been very great, but at least it has been recognized that the diseased kidney is not at fault in every instance and that there are lesions in the liver that may have some etiological bearing. In a search for the specific cause of nephritic toxicosis two directions have been followed: the one ascribing it to mechanical factors, the other to some chemical poison.

Edema of the brain, as suggested by Traube, has already been taken up in discussing the older views on uremia, up to 1882. Cohnheim at that time could not substantiate Traube's claim and nothing of note has been added to the discussion since that date. From all the personal reports the author has been able to gather neither spinal puncture nor decompression has any influence on relieving the symptoms; this would indicate that the increased intracranial pressure, resulting from a possible cerebral edema, was not a factor in the nephritic toxicosis.

Sodium chlorid has at times been accorded the blame for toxic manifestations accompanying Bright's disease. The one author usually cited as declaring in favor of this theory is Bohne, who came to his conclusions after injecting salt into animals. Hofmann, with good reason, criticizes these experiments and does not see why sodium chlorid and uremia should be regarded as cause and effect. That an excess of salt in the body will result in severe symptoms may be seen in the following instructive case report of Campbell (quoted by Volhard). Through an error a boy of five years received a rectal injection of water containing 450 gm. of salt per liter; headache, thirst, vomiting and bloody stools came on rapidly; within one half hour there was unconsciousness and within 5 hours, after many convulsions, the patient died. In regard to salt, as is true for many substances, almost any side of the uremic question may be given a semblance of probability if experiments are properly devised. The researches of Grünwald may be cited as demonstrating the exact opposite of what Campbell's fatal case would indicate. Grünwald found that rabbits fed on a diet very low in chlorin give up an excess of chlorids after diuretin; such a loss of salt results in convulsions and death. Widal, according to the substances retained by an insufficient kidney, divided renal disturbances into two classes, the chloremic and the azotemic types. The symptoms characteristic of the latter brought on by an increase of urea and other protein derivatives are those found in the disease described in the previous section under the heading of renal insufficiency. In the chloremic type, symptoms characteristic of the nephritic (convulsive) toxemia may be present. These are explained by assuming that the salt and water retention bring about edema of the lungs, gastro-intestinal tract, central nervous system, etc., and thus are responsible for dyspnea, vomiting, diarrhea, headache, Cheyne-Stokes' breathing, convulsive seizures, etc. That the symptoms of irritation of the central nervous system are not necessarily associated with cerebral edema has already been shown in the section giving Cohnheim's views in 1882; furthermore, some of the nephritic toxemias exhibit their symptoms in the absence of edema. To ascribe convulsive seizures, etc., to the mechanical effect of water retention induced by insufficient salt elimination does not meet the objections previously outlined, and sodium chlorid cannot be considered to be the sole cause of nephritic toxemia.

Golla, working on the theory that the convulsive and other phenomena in the nephritic patient should be due to some body formed as a result of abnormal metabolism, took up the problem of further investigation of *trimethylamin* in nephritis. He demonstrated a considerable increase of trimethylamin in the blood of uremics and a slight increase in the urinary output. His final conclusion may be given in his own words: "It is, however, hard to believe, even allowing for long continued action, that

trimethylamin in the amounts demonstrated in uremic blood is sufficient to account for the uremic convulsions."

Cholin and neurin, Golla believes, cannot on the present evidence, be accepted as poisons responsible for the convulsive symptoms attending nephritis. The possibility that neurin may be the causative agent has, however, not been exhausted.

Foster(*c*)(1921) isolated an unidentified *organic base,* which was toxic for guinea pigs, from the blood of patients suffering with "epileptiform uremia." This poison could not be obtained from the blood of normal persons. Foster believes that this substance may be the cause of nephritic toxicosis, though he has not yet obtained it in sufficient quantities to analyze it.

Ascoli supposed that the poison responsible for nephritic toxicosis was to be found in *nephrolysins.* Various other hypotheses concerning substances derived from the kidney have been offered but essentially they amount to a statement of the particular author's belief and have nothing further to recommend them.

Hartman has advocated *urinod,* a substance isolated from the urine, as a possible contributing factor toward nephritic toxicosis. This is a cyclic compound (C_6H_8O); its exact formula is unknown.

Summary

What has been ordinarily described and considered as uremia has been divided into three groups.

1. Conditions hitherto often erroneously classified as uremia, notably cerebral arteriosclerosis.

2. Poisoning due to *renal insufficiency.*

3. Poisoning, accompanying Bright's disease, whose characteristic symptoms appear to be the result of irritation of the central nervous system, which is not necessarily accompanied by renal insufficiency or retention of urinary excretory products, and which has been termed *nephritic toxicosis.*

The cause of the symptoms, erroneously classified as uremia, is frequently cerebral hemorrhages or areas of cerebral softening and possibly transient cerebral ischemia due to spasm of the corresponding arteries.

The factor which frequently brings about a fatal termination in renal insufficiency is acidosis due to the retention of the acid phosphates.

The attempts to associate either a particular substance which the kidney excretes in insufficient amounts or some toxic material which is the product of an abnormal metabolism have all been unsuccessful, with the possible exception of the acidosis just alluded to. It must be recognized that toxic symptoms may be produced by the sudden and excessive admin-

istration of almost any material contained in the body. Thus a number of investigators have found that injections of large amounts of urea are fatal (Hammond, Grehant and Quinquaud, Herter and Wakeman(*a*)); even such symptoms as vomiting, restlessness, opisthotonic convulsions, rapid respirations, coma and death were produced in such experiments (Marshall and Davis). Yet, judging the effect of urea from the clinical point of view, this substance will not result in untoward symptoms. The same apparent discrepancy may be noted in regard to the much quoted experiments of Landois. He found that creatin, urates, etc., applied to the cerebral cortex caused convulsive seizures and coma in animals. The conclusion which may be drawn from these facts is that the accumulation of various crystalloids in the blood and tissues may result in disturbed osmotic relations that produce the symptoms considered to be characteristic of uremia. It is perfectly obvious that the rapid rise in such substances may produce effects that will not be manifest if they accumulate slowly and allow adjustments in the osmotic processes of the body to establish themselves. This explains the difference between injection and ingestion experiments and the clinical phenomena accompanying renal insufficiency. Such osmotic effects of heaped up crystalloids in the body may be a contributory factor in the poisoning characteristic of renal insufficiency.

The cause for nephritic toxicosis evidently has not been determined or even remotely approached. However, this appears to be certain, that the same factor which results in the toxic (uremic) symptoms in this form of poisoning is also responsible for the nephritis, and that the toxic symptoms are not dependent upon the renal disease, as has been so frequently assumed. In other words both the Bright's disease and nephritic toxicosis are brought on by the same metabolic disturbance of unknown nature.

Increased Arterial Pressure in Nephritis

An increased blood pressure has been regarded as a characteristic sign of nephritis ever since Bright(*c*), in 1836, noted that cardiac hypertrophy and dilatation accompanied diseases of the kidney. It has been thought that such a blood pressure was a phenomenon which compensated for diminished kidney function by forcing the renal parenchyma to greater activity. This is the obvious conclusion that is necessarily come to at first glance. As clinical and experimental evidence have accumulated it has become evident that this interpretation is incorrect and that another solution of this problem must be looked for.

There are two considerations that make it doubtful whether a discussion of increased arterial pressure should be taken up in an article on the metabolism of nephritis. In the first place, the cause of hypertension may possibly not be dependent upon a metabolic disturbance, and in the second

place, there is very much to be said for Krehl's point of view which he voices somewhat as follows: "I could understand it if any one maintained that nephritis has no influence whatsoever upon the circulation—I almost believe this myself. This at least is true: neither the localization of the lesion in the kidney nor the extent of renal involvement is of any significance. It is only through functional disturbances that the kidney may be considered as being a factor."

However, inasmuch as nephritis is frequently accompanied by hypertension, and there are certain theories that ascribe the cause of increased blood pressure to a metabolic disorder, it is worth while to consider this subject in this section of the present book.

Occurrence of Increased Arterial Pressure in Nephritis.—An increased blood pressure has been noted in all forms of nephritis; at the same time, it must be borne in mind that the opposite is equally true, namely, that all types of kidney disease have been observed when hypertension was not present. Any arguments therefore based on the fact that one or the other forms of Bright's disease is accompanied by hypertension, or vice versa, is not conclusive.

Acute Nephritis.—True acute diffuse nephritis is supposed to exhibit an increased blood pressure, at least for a short period. It may be present for only a day or two or persist indefinitely. The height reached varies considerably. Janeway (*c*) observed that hypertension was not always present but may rise as high as 190. Rolleston, Weigert (*b*), Butterman and many others have noted similar findings, the hypertension in some instances reaching a level of 240 mm. of mercury. According to Volhard the blood pressure is more frequently below 160 than above this level. It therefore does not usually reach the very high figures associated with essential hypertension.

Volhard is largely responsible for the present attitude of many in regard to the problem of blood pressure in acute nephritis; some of his statements concerning it may therefore be of interest: "The pathognomonic symptom of the typical diffuse glomerulonephritis is an increased arterial pressure. When it is present in the course of an acute renal condition the diagnosis of an acute nephritis may be made without reservation and a focal nephritis or a degenerative nephrosis excluded, unless bichlorid of mercury poisoning and a hypertension as the result of anuria are present." These are very sweeping statements and if the differential diagnosis between an acute diffuse nephritis and a nephrosis depends upon the blood pressure readings, of course, there is no argument against it. However, the experience of some of the authors mentioned above and most clinicians is that hypertension is not a constant accompaniment of acute nephritis. Munk, in his recent work on nephritis, agrees with the last statement.

Nephrosis.—The degenerative lesions of the kidney have been termed nephrosis to distinguish them from acute diffuse glomerulonephritis.

This differentiation from the clinical point of view depends largely upon the fact that in nephrosis blood pressure is not raised above the normal level while in acute diffuse nephritis it is. In most instances this is correct. When there is an acute toxic lesion in the renal epithelium as occurs with arsenic, bichlorid of mercury or phosphorous poisoning, or with some of the acute infections as diphtheria, sepsis or typhoid fever, no hypertension develops (Krehl(*c*)(*e*)).

On the other hand, in some cases of bichlorid of mercury poisoning when anuria develops, the blood pressure may rise (Janeway, Volhard). This may be explained on the basis that extreme renal insufficiency will raise the arterial pressure irrespective of the type of kidney lesion. The kidney affections characteristic of pregnancy are of the nephrosis type. In this condition a marked rise of blood pressure, which evidently precedes the development of albuminuria, is usually found. It seems probable that this is an instance in which the hypertension and the renal disease depend upon the same cause and that the rise in blood pressure is not brought about by the kidney lesions. Some of the experimental animal nephroses have been accompanied by a slight increase in arterial pressure; this has been found in uranium, mercury, chromate and cantharidin poisoning (Zondek(*a*), Mayet, Mosenthal(*a*)).

Chronic Diffuse (Parenchymatous) Nephritis.—Hypertension is absent in many cases of chronic diffuse nephritis. This is the finding of Butterman to which the author agrees. In this type of nephritis, there is marked albuminuria and no renal insufficiency except the retention of water and salt at times. Volhard, in contradistinction to what has just been stated, believes that increased blood pressure is a necessary accompaniment of this form of kidney disease. Even he admits that the blood pressure usually drops to normal during rest in bed; until the arterial tension rises, when the upright position is resumed, these cases are not to be differentiated from "those partially healed instances of chronic diffuse nephritis that exhibit a 'Restalbuminurie' and the chronic glomerulonephritis of the focal infectious type." Here, as in acute nephritis, it may be said that if we regard an augmented blood pressure as a pathognomonic sign of chronic diffuse nephritis the truth of Volhard's conceptions is self-evident, otherwise we are privileged to believe that the blood pressure may continue at a normal level during the course of this malady.

It is well established that the height of the blood pressure usually does not rise above 180 mm. of mercury, and very rarely above 200 (Volhard and Fahr).

Secondary Contracted Kidney.—Clinically and anatomically, it is at times extremely difficult to differentiate the sclerotic, contracted kidney which is the end result of acute and chronic diffuse nephritis (secondary contracted kidney) from that following arteriosclerosis (primary contracted kidney). Under the circumstances it is not to be wondered at that

our knowledge concerning any sign, such as blood pressure, in this form of Bright's disease must necessarily be inconclusive.

Janeway found some of these cases to have extremely high blood pressure; Roth observed some without any increase in arterial pressure. The records have fluctuated between these two extremes. Most instances of true secondary contracted kidney which the author has examined have had a slight hypertension, the blood pressure usually being between 160 and 180, and frequently dropping to a normal level with rest in bed. It is probable that one of the distinguishing features of this form of contracted kidney is the comparatively low arterial pressure.

Essential Hypertension and Primary Contracted Kidney.—One of the most important facts in clinical medicine that has been developed within the last decade is that the most frequent and marked examples of arterial hypertension occur in the absence of any renal involvement. It is to the credit of Sir Clifford Allbutt(*a*), more than to any other one man, that this has been established. His clinical studies have been amply borne out since tests for renal function came to be applied to this problem. It is a daily experience to find patients whose systolic pressure ranges between 200 and 250 mm. of mercury and whose kidneys are normal to all the usual tests for renal efficiency. As time passes the strain upon the arterial system results in arteriosclerosis. Among other organs, the kidneys become affected and arteriosclerotic kidneys are the almost invariable finding in such cases. Such postmortem evidences were regarded as proof of the causative relation of a primary contracted kidney to hypertension. However, the clinical studies, as briefly outlined above, indicate clearly that the cart has been put before the horse and that the hypertension is the primary factor.

Some of the older anatomical findings in regard to this condition are of extreme interest. They have been duplicated frequently and may be regarded as correct. Jores demonstrated that a marked degree of arteriosclerotic kidney may be present and not be accompanied by hypertension (Jores, Krehl, Janeway, Schlayer). The opposite apparently also holds true: that an increased blood pressure may exist in the absence of any kidney disease whatsoever; it is worth noting that the actual count of the number of glomeruli destroyed bore no relation to the level of blood pressure (Jores(*b*)(*c*), 1908). Furthermore, as the late Theodore Janeway was very fond of insisting, the relation between a glomerular lesion and hypertension must be very remote since a low blood pressure is characteristic of amyloid disease, a condition in which the glomeruli are very extensively involved.

The problem of the relation of blood pressure to arteriosclerosis is too far removed from the subject matter of this article to warrant its discussion in detail; from what has been stated above it is perfectly evident, however, that a contracted arteriosclerotic kidney will not result in in-

creased arterial pressure, but that increased arterial pressure may result in an arteriosclerotic, contracted kidney.

The Cause of Increased Arterial Pressure in Nephritis

The exciting cause of increased arterial pressure is unknown with the exception of the fact that lead poisoning is frequently associated with a hypertension. The classification of the theoretical possibilities, that may be responsible for a rise of blood pressure, has often been attempted, and the material subdivided under the heads of chemical, mechanical, etc., factors. This is an extemely artificial arrangement and it is preferable simply to state the facts as they have been developed thus far without forcing the material into an orderly but unnatural and illogical sequence.

One probability has been almost completely lost sight of. This is that there is almost assuredly more than one cause for hypertension. It would be very strange if the raised level of blood pressure in acute nephritis, lead poisoning, essential hypertension, toxemia of pregnancy, etc., were all due to the same pathological physiological disturbance and yet this is not uncommonly assumed to be true.

Insufficient Renal Function.—It has been previously mentioned that in some cases of bichlorid of mercury poisoning, associated with anuria, the blood pressure may rise slightly. This is not true in all instances of this sort; why it should occur in some cases and not in others is not clear.

A reduction of kidney substance in experimental animals results in a rise of arterial pressure (Passler and Heinecke, Janeway(*c*)). In addition such animals showed a marked polyuria (Bradford). Janeway found that the blood pressure in a patient rose to 180 when the only remaining kidney was excised. On the other hand in animals, extirpation of both kidneys causes no notable changes in the arterial tension.

A partial obstruction of both ureters may bring about an increased blood pressure. Cohnheim demonstrated this many years ago. However, there are cases in which the blood pressure does not change. When such an obstruction becomes complete the pressure may rise markedly, as high as 210 on the third day of anuria (Passler(*b*), Brasch). A temporary ligature of the ureters produces a contracted kidney and a hypertension (Beckman, Strauss, Rautenberg).

It is curious that the marked renal insufficiency so commonly seen in congenital polycystic kidneys is not necessarily associated with a blood pressure above the normal (Means and Rogers). The author has seen a similar patient, observed for about two years.

Prostatic obstruction apparently may be responsible for an increase in blood pressure, which has a tendency to subside as the conditions are restored to normal, by retention catheters or operative means (O'Conor,

Monakow and Mayer). Both the amount of residual urine as well as the diminution of renal function appear to be instrumental in bringing about these changes (O'Conor). The actual cause of the rise of blood pressure in these cases can only be surmised (Monakow and Mayer).

It has been argued that the waste products which accumulate in the blood when renal insufficiency exists may be the cause for hypertension. The present methods of blood chemistry have shown very definitely, as far as the non-protein nitrogenous constituents, urea, uric acid, creatinin, etc., are concerned, that this is not correct. There may be maximal accumulations of these substances in the blood without increase in blood pressure and vice versa.

In summarizing the effect of renal insufficiency upon blood pressure, it must be acknowledged that diminished kidney function, whether the cause resides in the kidney itself or the ureters or urethra, may at times result in a hypertension but this is not a constant phenomenon. Why this should be so it is impossible to state at the present time. One statement of Janeway, which shows how wide an interest this subject has for clinical medicine, is that he believes it possible that the hypertension found in some instances of heart failure may be due to insufficient kidney action brought on by passive congestion.

Blood Volume and Plethora.—Keith, Rowntree and Geraghty found that there was no causal relationship between blood volume and hypertension. When the total quantity of the blood increases under any circumstances, as occurs in certain states, and may be artificially brought about by transfusions and infusions, in the human subject, there is no rise in the blood pressure. The vasomotor control of the arteries appears to be such that it can regulate the pressure of the fluid within them and maintain it at a constant level regardless of the actual volume of fluid.

It was shown some years ago by Cohnheim and Lichtheim that plethora does not increase blood pressure. Volhard believes that this statement may apply to acute plethora but not to chronic. However, every case of long standing edema does not exhibit an augmented blood pressure; in fact the majority do not.

Viscosity of the Blood.—An increased viscosity of the blood must be considered as a possible causative factor of arterial hypertension in nephritis. The fact that such a change entails more resistance to be overcome by the heart is self-evident. It must be borne in mind, however, that a dilatation of the peripheral arteries may compensate for the factors just mentioned and that the blood pressure may therefore be maintained at a normal level in spite of them. The finding of Lucas, that there is a hypertension in only about thirty per cent of the cases of erythemia described by him, bears this out. The whole question may be considered as set aside, for the present at least, by the observations of Hirsch and Beck who showed that an increased blood viscosity did not exist in nephritis.

Increased Vasomotor Tone.—That an increased tonicity of the peripheral vessels will result in a rise of blood pressure, provided the heart's force and the blood volume remain constant, requires no proof. Such a change in function, frequently spoken of as "spasm of the peripheral vessels," is generally conceded to be the most likely explanation of the occurrence of an increased arterial pressure. In a measure, this theory can not be considered to answer the problem completely for it still remains to be determined what the agent or agents are that influence the blood vessels in this way, and furthermore it does not satisfy the query as to where the stimulation occurs, in the nervous system or in the walls of the arteries themselves: it is important to be thoroughly informed regarding both of these points before the problem may be considered even as approaching a solution.

Gull and Sutton originally advanced the idea that an organic lesion which narrowed the lumen of the smaller arteries was the cause of hypertension. Such a pathological process will in all probability result in an increased arterial pressure. However, this state of affairs is a rare exception and not the rule, for the smaller blood vessels in hypertensive states maintain their ability to contract and dilate much as in normal individuals. This has been demonstrated by the good reaction such patients exhibit to the vasodilators (Janeway, Matthew, J. Miller, Wallace and Ringer), by the remarkable drop of the hypertension (often 50 mm. of mercury) with rest, even over a period of only a few minutes and a corresponding rise on excitement, as shown by a number of observers (Hensen, Israel and others) and recently brought out by Boas and by O'Hare, and by the occurrence of sudden extreme elevations of blood pressure, termed "Gefässkrisen" by Pal.

It was at one time believed that if a part or all of the renal circulation were shut off that hypertension would result because of a compensatory effort on the part of the body to effect renal secretion. However fascinating this may be in theory, it is not borne out by the facts in the case; complete extirpation of the kidneys, or ligation of both renal arteries does not result in an increase in the blood pressure; partial occlusion of the renal circulation was supposed by some to bring this about (Katzenstein) but a repetition of these experiments has failed to substantiate the original observation (Alwens, Senator(*l*)). It may be worth noting again that the most frequent and marked instances of hypertension occur when there is no involvement of the kidney whatsoever. Another idea advanced in this connection is that fathered by Johnson who believed that the retention of renal excretory products was the cause of the increased vascular spasm. As far as this hypothesis can be judged, by means of the non-protein nitrogenous constituents of the blood as a criterion, it is incorrect since the arterial pressure in any case apparently remains unchanged whether the blood urea is markedly increased or drops to normal (Mosenthal(*f*)).

The impression that hypertension is characteristic of the uremic state (Muller) is not substantiated by observations. A recent case of secondary contracted kidney dying in uremia with a urea nitrogen well over 100 mg. per 100 c.c. of blood showed a systolic blood pressure of approximately 120 to 130 mm. of mercury and no higher for several weeks before death. This is not an unusual occurrence. The bare fact remains that most clinicians and investigators interested in blood pressure problems believe that increased vasomotor tone is responsible for the hypertension characteristic of Bright's disease, as well as of those states in which the arterial tension assumes a higher level independently of any renal disease. This is based largely on the very definite evidence that the musculature of the arteries is overactive in these cases and that the blood pressure shows very marked variations on slight provocation. There may be other substances, besides those already considered, which will increase the vasomotor tone and consequently be responsible for a rise in blood pressure. These will be taken up under separate headings in the following paragraphs.

Suprarenal Secretion (Epinephrin).—The explanation of hypertension in nephritis that meets all theoretical demands, more perfectly than any other, is the one that attributes increased vascular tone to an excess of epinephrin in the blood. Not only blood pressure changes but also the occurrence of hyperglycemia in Bright's disease may be attributed to this cause. Much time and effort have been spent in bringing positive proof of the overactivity of the suprarenal glands in this connection. Thus far such attempts have been barren of any positive results. Janeway summarized the work of others and his own researches on this subject and came to the conclusion that there was no adequate method to demonstrate epinephrin quantitatively in the blood. Such a state of affairs naturally must leave the problem of the relation of the suprarenal glands to hypertension in nephritis an open question, however tempting it may be to assume, from a theoretical point of view, that there is an overproduction of the internal secretion of the suprarenal gland to account for an increase in vascular tone and hypertension.

The idea that the overactivity of the suprarenal gland is responsible for hypertension was initiated by Neusser and Wiesel who found an increased blood pressure in two cases of carcinoma of the adrenal glands. Volhard showed that a similar state of affairs could exist in hypernephroma. The French have been particularly enthusiastic in indorsing this theory. Schur and Wiesel injected another element into this matter when they proposed that the retention of the waste products ordinarily excreted by the kidney stimulated the adrenals to increased activity. However, here, as in many other instances in which an accumulation of urea, etc., in the blood is considered in causative relation to augmented blood pressure, it must be recognized that there are many patients in whom the blood chemistry shows a marked rise in the urinary excretory products without

any changes from normal in the blood pressure. Schlayer(*a*), after testing artery strips with the blood sera of normal and hypertensive patients, came to the conclusion that by this method there was no proof that there is an increased suprarenal secretion that can be considered as a cause of hypertension. In the discussion on carbohydrate metabolism in nephritis it has already been mentioned that Neubauer suggested that epinephrin in excess of normal might be responsible for the hyperglycemia characteristic of some cases of Bright's disease.

There are many further citations that could be alluded to in regard to the problem of adrenal activity in relation to Bright's disease especially concerning the question of hypertension. It is very tempting to believe that this theory represents the actual state of affairs, as the whole matter would thus be explained in a most satisfactory manner. However, until definite proof of the actual occurrence of adrenalinemia is furnished by the development of suitable methods, the matter must remain a theory, and not an accomplished fact. It is extremely interesting to note that from an experimental point of view the hypothesis of hyperadrenalinemia as a cause for increased blood pressure may be entertained. Kretschmer showed how small constant doses of epinephrin maintained a hypertensive state in rabbits.

Internal Secretions Derived from the Kidney.—Many attempts have been made to associate various manifestations of nephritis with the absorption of material derived from the kidney itself. Brilliant as this possibility is on first thought it has thus far proved itself to be more fanciful than real. Great care must be exercised by those interested in this particular problem that a fertile imagination does not wander further from the path of rational thought than the facts in the situation warrant.

"Renin" was the term applied by Tigerstedt and Bergman (1898) to a substance obtained from the rabbit's kidney which when injected into animals produced a rise of blood pressure. Bingel and Strauss confirmed this and Shaw enthusiastically endorsed the idea of the origin of some pressor substance from the kidney itself. Bingel and Claus, on the other hand, did not find any greater amount of this product in diseased than in normal kidneys and furthermore the later researches of Pearce and J. L. and E. M. Miller show that the kidney does not contain a pressor substance and that the internal secretion of the kidney does not furnish such a material.

From the clinical point of view it has been urged that degenerative and inflammatory products resulting from corresponding processes within the kidney may be responsible for hypertension. This does not agree with the facts as they are known to-day for the most marked and constant examples of increased arterial pressure are those that are found at first as hypertension without any renal involvement and in their later stages as complicated by arteriosclerotic kidneys. Those forms of Bright's disease

characterized by marked breaking down of kidney substance, the nephroses and acute and chronic diffuse nephritides, are not inevitably accompanied by high blood pressure. Janeway believes that, "This fact, to my mind, so argues against the hypotheses that have been cited that I think it is reasonable to dismiss them from consideration." The burden of proof in solving the problem of the relation of a possible internal secretion of the kidney to hypertension certainly must be assumed by the advocates of this rather fanciful contention.

The Influence of Food Products on Blood Pressure

There have been researches without number on this subject. Most of them have lost sight of the fact that physical and especially mental relaxation are of the greatest importance in their influence upon lowering blood pressure. The observations in most instances concern themselves with patients in bed or under supervision in sanatoria and all the results obtained are attributed to the diet, which is not correct. Moreover, the dietetic control in most instances is far from ideal and usually does not measure up to the required standards of accuracy.

Sodium chlorid, proteins and purins have all been accredited with the attribute of pressor substances.

Sodium Chlorid.—There have been many attempts to attribute a causal relation between the salt intake and blood pressure. Lowenstein, among others, believed that this was not correct and the general experience has been that patients on a bland, salt free diet did exhibit a reduced blood pressure while at rest but that the hypertension again manifested itself when normal activity was resumed. A very good illustration of this sort was a middle aged man suffering with mild diabetes, albuminuria and a systolic pressure of 240 mm. of mercury. He was placed on a salt free diet, which was conscientiously carried out as determined by the progressively lower output of salt in the twenty-four hour specimens of urine. The systolic blood pressure dropped to 130 and remained at that level for some time. The patient was then allowed to get up and gradually resume his former occupation. The blood pressure slowly rose approaching its former height although the diet was unchanged. The relief from physical and mental strain were doubtlessly the factors that were effective in reducing the hypertension; the restriction of the sodium chlorid apparently had little influence. Recently Allen(*d*) has revived the idea that salt is responsible for an increased blood pressure and that very marked effects may be produced by the ingestion of ten grams of sodium chlorid. Some of this observer's cases have a low blood chlorid content; furthermore, in many patients a paroxysmal rise of blood pressure may be witnessed without the administration of salt so that it is certain that salt is not the only factor concerned. Furthermore, J. H. Short and the author have

attempted to duplicate Allen's results and have not succeeded in raising the blood pressure by the administration of ten grams of salt. It is probable that the influence of rest, relief from nervous strain, and confidence in the treatment are the elements that relax the blood vessels and lower the blood pressure, and that the sodium chlorid in the amounts in question is of very little or no importance.

A low protein diet is not effective in lowering blood pressure or a high protein diet of raising it. At least this is the case in observations carried out over a period of few weeks (Mosenthal(*f*)). A sub-caloric régime pursued in normal persons for a long time will result in a lowering of blood pressure (Benedict and collaborators). This phenomenon is accompanied by a depression of the vitality and efficiency of such individuals and the diminished arterial tension is probably an expression of the general state rather than a specific effect of low protein feeding. The work of Hecht and Loeb(*a*) are often quoted in this connection, but neither the results obtained nor the methods of observation in these papers are sufficiently striking to draw any specific conclusions as to the effect of diet upon blood pressure.

As to the influence of *purins* upon arterial tension, it may be sufficient to quote the experience of Sir Clifford Allbutt(*a*) in this connection: ". . . again and again I have placed high-pressure patients on purin-free diets, or on vegetarian diet with cheese, milk and eggs, with no appreciable reduction of blood pressure within such limit of weeks as to satisfy the conditions of an experiment."

Recently the author has seen a few cases in which a reduction of an excessive *carbohydrate* intake, as indicated by a high blood sugar in non-diabetic patients, resulted in a material reduction of blood pressure. Whether these were accidental relations or are of any real significance remains to be determined.

In conclusion, it may be said that at present there are no definite facts that point to any of the food substances as having a causative relation to blood pressure. Much remains to be accomplished in regard to this problem, as most of the observations thus far published, although very numerous, lack accuracy and proper control periods.

Lesions in the Glomeruli

This subject deserves brief mention inasmuch as Volhard has lately stressed glomerular lesions as the main cause for increased blood pressure. He believes that the effect of the blood flow through the glomeruli has a reflex influence upon the other vessels in the body; when there is any interference with the current flowing through the glomerular capillaries, an increased tone of the arteries and arterioles is brought about through reflex paths and hypertension is the result. When there are no glomeruli

present—as in double nephrectomy—the reflex can not be elicited. (It should be noted, however, that there may be a slight rise in blood pressure under these circumstances, as in Janeway's case, in which the blood pressure rose to 180 after extirpation of the only remaining kidney.)

Volhard cites the fact that in focal nephritis and in the nephroses, that is when there are sufficient glomeruli intact to allow the blood to pass through the kidney freely, there is no rise in the blood pressure. On the other hand, in acute, subacute and chronic diffuse nephritis the narrowed lumina of the glomerular capillaries set up a reflex that stimulates the arteries to increased tone and results in raising the blood pressure. The hypertension is thus regarded as a compensatory phenomenon to induce an adequate renal circulation. Such an explanation is identical with that held twenty years ago and which has not proved to be entirely satisfactory, inasmuch as it has not been found that renal function is modified in any way as the blood pressure varies. The studies that have been made on patients whose systolic pressure changes a good deal amply bears this out.

There are certain other facts with which this theory is not in accord. In amyloid disease, in passive congestion, with partial occlusion of the renal veins by pressure or otherwise, and in some instances of arteriosclerotic kidney (as previously mentioned) the blood pressure rises slightly, if at all, yet in all of these glomerular circulation should be impeded. Furthermore, the condition, characterized by the most marked degrees of blood pressure, shows in its early stages at least a normal renal structure. It is certain that in this condition, essential hypertension, Volhard's theory can not be applied; whether or not it holds true for the other types of hypertensive disease can not be denied, though it seems improbable that it should.

To what different conclusions a clinician and pathologist may arrive at is illustrated by the deductions which Ophüls draws from his pathological material. He found in a series of autopsies showing chronic glomerulonephritis that there were more instances of low blood pressure and small hearts among the cases with the most extensive destruction of renal tissue than among those in which the renal lesion was less marked.

Summary

An increased arterial pressure may occur in any form of Bright's disease; it may be absent in any of them. It is more common in the acute, subacute and chronic diffuse cases of nephritis than in the degenerative lesions or nephroses in which it does not appear frequently. The most marked instances of hypertension are those characteristic of the malady called essential hypertension, in which the kidney lesions (arteriosclerosis) are secondary to the increased blood pressure, and not primary. In fact

an arteriosclerotic kidney (brought on by other causes than hypertension) may exist without a concomitant rise in arterial pressure.

The pathologicophysiological process that is responsible for hypertension appears to be an increased vasomotor tone of the smaller arteries. This anomalous condition maintains the blood in the arterial tree under an abnormal degree of tension. The variability of the blood pressure in the hypertensive states, as shown by the reaction to vasodilators and the rapid drop with physical and especially with mental relaxation, indicates that the musculature of the arterial walls is not injured and that the older conception of a fibrosis of the smaller blood vessels is not an adequate explanation to account for an increased peripheral resistance in the arterial circulation in most instances.

The cause for the increased vasomotor tone has not been determined. Insufficient renal function, increased blood volume, increased blood viscosity, hyperadrenalinemia, internal secretions derived from the kidney, intoxication from food products (salt, proteins, purins), and reflexes from partially occluded glomeruli have all been considered in the light of etiological factors that might stimulate the tonicity of the arteries, but none of them have up to the present time fulfilled all the requirements necessary to make it clear that they are the dominating element in hypertension. There is only one known poison that causes high blood pressure. This is lead. It is probable that there is not one cause but many that may be considered to be responsible for a raised arterial pressure. It would be very strange if such conditions as toxemia of pregnancy, lead poisoning, essential hypertension, etc., should prove to have the same toxic substance to which the increased tonicity of the arterioles could be attributed.

The Metabolism in Gout . . . . . *Joseph H. Pratt*

Introduction—The Purin Bodies—Nucleo-Proteins, Nuclein, and Nucleic Acid—Animal and Plant Nucleic Acids—Hydrolytic Products of Nucleic Acid—The Formation of Uric Acid from Nucleic Acid—Synthesis of Nucleic Acid and Uric Acid—The Source of Uric Acid in the Urine—The Effect of Purin-containing Food on the Output of Uric Acid—Uric Acid in the Blood in Health—Uric Acid in the Organs and Tissues—Uric Acid in the Blood in Gout—Uric Acid in Joint Exudates in Gout—Uric Acid in the Tissues in Gout—The Urine in Gout—Action of Phenylcinchoninic Acid (Atophan, Cinchophan) in Gout—General Metabolism in Gout—Theories of Gout—The Renal Theory—The Ferment Theory—The Combined Uric Acid Theory—Tissue Retention Theory—Treatment—Diet in Acute Gout—Diet in Chronic Gout—Atophan Therapy—Colchicum—Other Methods.

The Metabolism in Gout

JOSEPH H. PRATT

BOSTON

Introduction

Gout is a disease associated with a disturbance of the uric acid metabolism. The one unchanging feature that characterizes the disease is the deposition of sodium urate in the tissues. This fact is the firm rock in the quicksands of theory.

An immense amount of work has been done during the past decade on the metabolism in gout with the aid furnished by advances in biochemistry and by the discovery of accurate methods of blood analysis. Many new facts have been acquired, but the statement von Noorden(*l*) made in summing up the state of knowledge of the subject in the second edition of his handbook in 1907, is still true in 1921:—"A clear insight into the nature of the disturbance of metabolism in gout has not been attained."

The doubt often expressed in the past as to whether uric acid is actually the *materia peccans* in gout has not been dispelled by recent investigations. Where the disease takes its origin is unknown. It may be in the kidney and result from renal retention of uric acid, as originally Garrod(*d*) thought. Many hold this view. The disease on the other hand may primarily be a disturbance of purin metabolism with secondary changes in the kidneys. This theory has the most adherents. A third possibility is that the disease begins in the joints themselves (Bass and Herzberg). An old theory recently revived to explain newly discovered facts is that gout has its basis in a special form of hepatic insufficiency (Chauffard, Brodin and Grigaut).

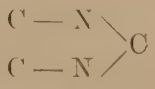
In view of the close relation between gout and uric acid it is necessary to make a study of nucleic acid metabolism in health and in disease with the hope that it will later reveal the exact nature of the disturbances in gout. Since the chemistry of nucleic acid and the purins is dealt with in another article in this work, we shall take up here only the chemical facts that are important for our discussion of gout. Chalmers Watson held that gout is an infection and that the toxin or toxins generated disturb metabolism in a way favorable to the deposit of uric acid. Llewellyn believes that local foci of infection give rise to gouty arthritis in individuals in whom there is an "inherent abnormality or instability of nuclein metabolism."

The Purin Bodies

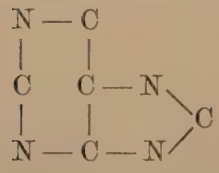
The relation of uric acid to a large group of compounds has been definitely established (E. Fisher(*b*)). They are all derivatives of purin (a word coined from purum uricum). The purin substances of the animal body with the exception of uric acid were formerly called nuclein bases (Kossel), alloxuric bases (Kossel and Krüger) or xanthin bases. The entire group including uric acid was embraced under the name of alloxuric bodies (Kossel and Krüger).

Purin may be considered as made up of two characteristic parts.

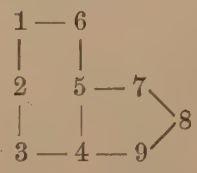
(1) A pyrimidin nucleus and

(2) An imidazol nucleus 

A condensation of these two rings gives the framework of purin.



To these constituent atoms numbers have been assigned (Fischer)



In this structure of the purin bases an acid is united to urea. This is called a *ureid*. If as in the case of purin there are two molecules of urea it is termed a *diureid*. From uric acid and the other purins two ureids can be obtained. One of these, parabanic acid, is a compound of oxalic acid and urea.

oxalic acid — urea — parabanic acid

The other ureid is alloxan, a compound of mesoxalic acid and urea.

urea — mesoxalic acid — alloxan

From these two reactions it is evident that purin must contain the rings of the pyrimidin nucleus and of the imidazol nucleus which when condensed form purin.

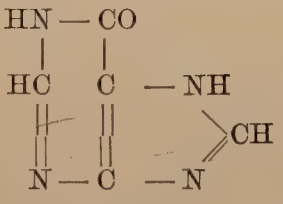
Purin is related to substances like cytosin and uracil, because of its pyrimidin group, and to histidin, a constituent of protein, because of its imidazol group.

The "alloxuric bases," hypoxanthin, xanthin, adenin and guanin (all discovered by Kossel) were shown by him to form the only source of uric acid.

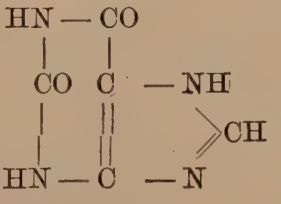
The investigations of Fischer made clear the relation of the purin bases to each other and to uric acid. The simplest member of the group is the hydrogen compound, purin ($C_5H_4N_4$) made up of the purin nucleus plus four atoms of hydrogen. This is not found free in nature. The addition of oxygen to purin causes the formation of hypoxanthin, xanthin and uric acid. If an atom of hydrogen is replaced by amid (NH_2) adenin is formed. If in addition there enters an atom of oxygen guanin results. Methyl groups join the nitrogen atoms and form methyl purins, theobromin, theophyllin and caffein.

In the formulas given below the situation in the purin ring of the atoms added is indicated by the number given by Fischer.

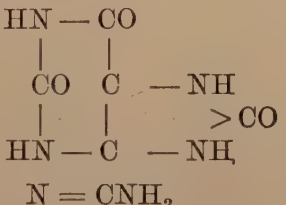
Hypoxanthin ($C_5H_4N_4O$) = 6 Oxypurin =



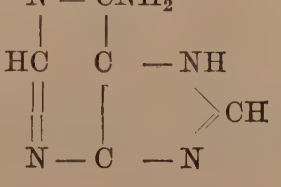
Xanthin ($C_5H_4N_4O_2$) = 2.6 Dioxypurin =



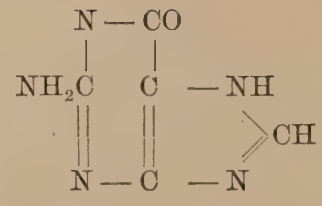
Uric acid ($C_5H_4N_4O_3$) = 2.6.8 Trioxypurin =



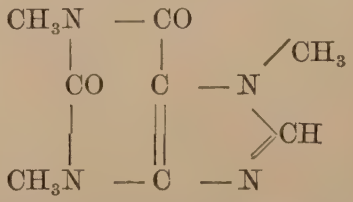
Adenin ($C_5H_5N_5$) = 6 Aminopurin =



Guanin ($C_5H_5N_5O$) = 2. Amino—6 oxypurin =

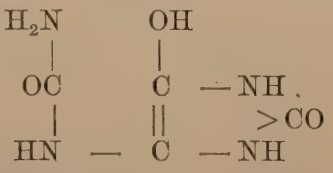


Caffein ($C_8H_{10}N_4O_2$ = 1 . 3 . 7 Trimethyl — 2.6 dioxypurin =



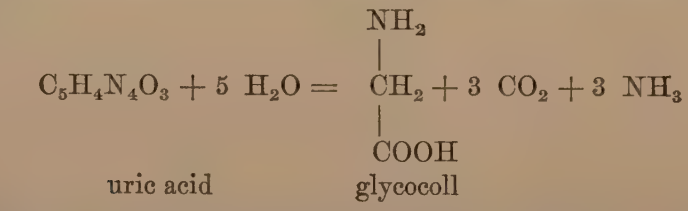
The close relation of uric acid to allantoin was recognized by Wöhler and Liebig. This substance had been previously isolated from the amniotic fluid of the cow. They found it could be obtained by the oxidation of uric acid. Although it does not contain the purin ring its relation to uric acid is shown in the structural formula:

Allantoin



Liebig and Wöhler also obtained alloxan and urea by the oxidation of uric acid with nitric acid. It was later shown that suitable oxidizing agents may convert uric acid into oxalic acid (Claus).

Uric acid when heated with concentrated hydrochloric acid in closed tubes is broken down into glycocoll, carbon dioxid and ammonia (Strecker).



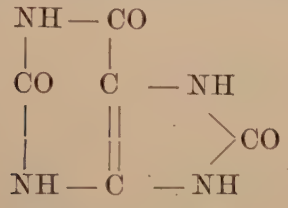
uric acid glycocoll

Uric acid can then yield four important decomposition products—glycocoll, urea, allantoin and oxalic acid. Allantoin is the only one of these four substances that is definitely known to be formed in the physiological destruction of uric acid, although Pincussohn(*b*)(1919) has presented evidence that oxalic acid may be one of the final products in the breakdown of purins.

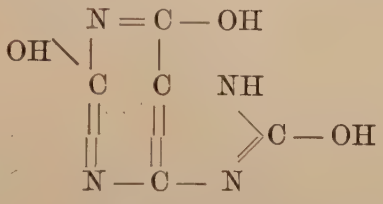
The synthesis of uric acid from urea and glycocoll has been produced artificially (Horbaczewski), but it could not be imitated by feeding these compounds. Medicus published the correct structural formula of uric acid

as early as 1875. This according to Walter Jones was a lucky guess, while Stanley Benedict regards it as a beautiful example of chemical prophecy.

With the amino- and oxypurins two tautomeric formulas are possible. The derivatives of the saturated purin are designated imino- and keto (lactam) compounds. Those looked upon as formed from the unsaturated purin are the amino- and enol (lactim) compounds.

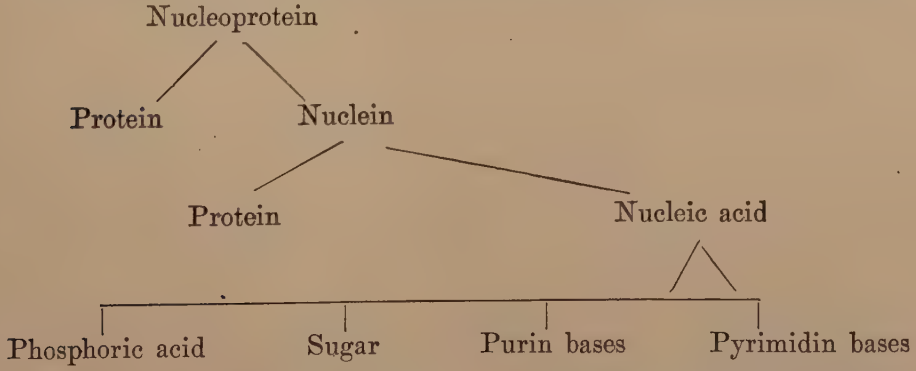


Lactam form of uric acid



Lactim form of uric acid

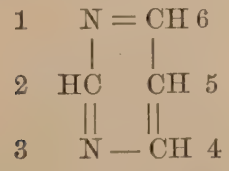
Nucleoproteins, Nuclein, and Nucleic Acid.—The purin bases are disintegration products of nucleic acid which is found in the nuclei of all animal and plant cells. This was Kossel's epoch making discovery. Nucleic acid is found in cells combined with various proteins. These compounds are the nucleoproteins. The proteins bound to nucleic acid are of the type of protamin and histon. They are thus chiefly composed of diamino-acids. The nucleoproteins when digested with pepsin-hydrochloric acid split off protein. The insoluble residue that remains is called "nuclein." This is probably a salt of protein and nucleic acid. Although resistant to peptic digestion nuclein by hydrolysis with alkalies is decomposed into protein and nucleic acid. By long continued boiling with 2 to 5 per cent sulphuric acid the nucleic acids break down into their primary constituents—phosphoric acid, sugar, purin bases and pyrimidin bases. The disintegration of nucleoproteins is shown in the following diagram:



The most characteristic constituents of nucleic acid are the purin bases. Protein contains no purin (Kossel). Only the amino-purins, adenin and guanin exist in the nucleic acids of plants and animals. By the deamini-

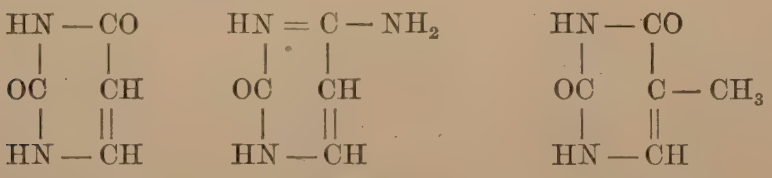
zation of the amino-purins in the organism the oxypurins, hypoxanthin and xanthin are formed. These by oxidation are converted into uric acid. Finally, in all animals except man and the ape uric acid is further oxidized into allantoin, the real end product of purin metabolism.

The second group of primary constituents of the nucleic acid molecule are the pyrimidin bases.



The formula shows that pyrimidin has the structure of an ureid, and that it possesses a part of the purin nucleus. Emil Fischer has produced pyrimidin synthetically from urea and acrylic acid ($CH_2 = CH — COOH$).

Kossel and his co-workers have found the following derivatives of pyrimidin in nucleic acids.



uracil
2.6 dioxypyrimidin

cytosin
2. oxy—6 aminopyrimidin

thymin
5 methyl—2.6 dioxypyrimidin

Animal and Plant Nucleic Acids.—There are two distinct types of nucleic acid, one of which is obtainable from the nuclei of animal cells and the other from the nuclei of plant cells. Kossel discovered the final hydrolytic products of nucleic acid by his studies of thymus nucleic acid and yeast nucleic acid.

Jones(*d*) gives the following table in his monograph on nucleic acids.

Hydrolytic Products of Nucleic Acid

Of Plant Origin	Of Animal Origin
Phosphoric acid	Phosphoric acid
Guanin	Guanin
Adenin	Adenin
Cytosin	Cytosin
Uracil	Thymin
Pentose	Levulinic acid

Nucleic acid is then a dehydrolyzed product of phosphoric acid, carbohydrate and four nitrogenous ring compounds. These eight substances are the fundamental groups of nucleic acids (Jones). The carbohydrate group in animal nucleic acid is represented by the decomposition product levulinic acid. This probably indicates a hexose precursor, but the particular hexose has not been discovered. Feulgen, however, claims that the carbohydrate group is not hexose ($C_6H_{12}O_6$), but glucal ($C_6H_{10}O_4$). Plant nucleic acid contains always uracil and pentose, while animal nucleic acid contains always thymin and a carbohydrate other than pentose. It is generally stated to contain hexose. The pentose in plant nucleic acid was found by Levene to be d-ribose.

Levene(*a*)(*b*)(*c*) has shown by his brilliant investigations that nucleic acid belongs to a class of substances to which he has given the name of "nucleotids." They are compounds in which a carbohydrate group links a phosphoric acid group with a purin or pyrimidin group.

Two mononucleotids have been obtained from animal tissues. These have long been known in physiological chemistry by the names of inosinic acid and guanylic acid. Inosinic acid was obtained from meat extract by Liebig in 1847. Levene and Jacobs found that it was composed of phosphoric acid and hypoxanthin united by d-ribose. It is then hypoxanthin nucleotid. Guanylic acid was discovered by Hammarsten in 1894. It was the non-protein constituent of a substance obtained from the pancreas and called β-nucleoprotein. Levene and Jacobs in 1909 proved that guanylic acid was composed of guanin united to phosphoric acid by the pentose d-ribose. Guanin nucleotid prepared from yeast by Jones and his co-workers did not differ from guanylic acid in any respect.

From the structural point of view these two mononucleotids may be regarded as simple nucleic acids. "Their groups are those of *plant nucleic* acid, and they cannot therefore be directly derived from the nucleic acid of the *animal* tissues in which they occur" (Jones(*d*)).

Guanylic acid has been prepared from yeast nucleic acid by Jones and Richards. Probably both inosinic acid and guanylic acid found in animal tissues are formed from the nucleic acid of plants taken as food.

Levene and Jacobs split the mononucleotids, guanylic acid and inosinic acids, by neutral hydrolysis under pressure into phosphoric acid and a compound, consisting of a pentose joined to a purin base. To this compound Levene gave the name "nucleosid."

$$\begin{matrix} HO \\ O=PO \\ HO \end{matrix}\!\!-C_5H_8O_3-C_5H_4N_5O + H_2O = H_3PO_4 + C_5H_9O_4.C_5H_4N_5O$$

guanylic acid — guanosin

Emil Fischer(*b*)(*d*) has reported the synthetic production of a nucleotid composed of the purin group theophyllin united by a carbohydrate

group to phosphoric acid. This constitutes the long sought synthesis of a nucleic acid, although the product is not identical with any known to occur in nature. Davis and Benedict have isolated from beef blood as a crystalline substance a compound of uric acid and pentose. This is a uric acid nucleosid, the possible existence of which had been suggested by the important discoveries of Levene.

The theory that yeast nucleic acid was composed of four nucleotids was presented by Levene(*d*) in 1909, and its correctness conclusively proved by Levene, Jones, Thannhauser, and their co-workers. All four of the nucleotids have been separated from yeast nucleic acid in pure crystalline form. Cytosin nucleotid by Thannhauser and Dorfmüller(*b*) in 1918, adenin nucleotid by Jones and Kennedy in 1918; guanosin nucleotid (guanylic acid) by Levene(*d*) in 1919; uracil nucleotid by Levene(*e*) in 1920. Levene has found that a mild hydrolysis with 5 per cent ammonia at a temperature of 100° C. breaks up yeast nucleic acid into its four mononucleotids.

Guanin Nucleotid $HO(HO)O{=}P - O.C_5H_8O_3.C_5H_4N_5O$

Adenin Nucleotid $HO(HO)O{=}P - O.C_5H_8O_3.C_5H_4N_5$

Cytosin Nucleotid $HO(HO)O{=}P - O.C_5H_8O_3.C_4H_4N_3O$

Uracil Nucleotid $HO(HO)O{=}P - O.C_5H_8O_3.C_4H_3N_2O_2$

Jones holds that the linkages of the mononucleotids is through the carbohydrate groups and presents experimental evidence in support of this view.

Yeast nucleic acid has been decomposed by neutral hydrolysis with the formation of four nucleosids (Levene and Jacobs).

Guanosin	$C_{10}H_{13}N_5O_5$
Adenosin	$C_{10}H_{13}N_5O_4$
Cytidin	$C_9H_{13}N_3O_5$
Uridin	$C_9H_{12}N_2O_6$

Levene [1] has recently prepared nucleic acid from the spleen, pancreas and liver. None of the samples contained pentose. The two purin bases adenin and guanin were present in each, but the amount was much greater in the spleen nucleic acid than in the others.

[1] Levene. "Preparation and Analysis of Animal Nucleic Acid," Journ. Biol. Chem., 1921, 48, 177.

The Formation of Uric Acid from Nucleic Acid

This is accomplished by means of a series of ferments. In the stomach by the action of the gastric juice nucleoproteins are changed into protein and nuclein, and from the latter a small amount of nucleic acid is formed, but it is not decomposed in the stomach (Abderhalden and Schittenhelm (*c*), 1906). Gastric juice and pancreatic juice do not cause any change in the physical and chemical properties of nucleic acid, according to Levene and Medigreceanu. Human duodenal juice obtained by means of a duodenal tube so changed yeast nucleic acid that it becomes easily soluble in water and dialyzable (Thannhauser and Bommes). Thannhauser and Dorfmüller(*d*) as a result of a careful study concluded that in the duodenum one mononucleotid is split off the tetranucleotid leaving a new substance, a trinucleotid. Levene(*f*) has shown that this supposed chemical compound is really a mixture of three mononucleotids.

The point of great physiological importance shown by Thannhauser is the conversion of nucleic acid without deep splitting of the molecule into substances that are easily absorbed from the upper part of the intestine. Levene and Medigreceanu(*b*) had previously shown that intestinal juice forms mononucleotids from yeast tetranucleotid, and the two purin nucleotids are converted into the two nucleosids, adenosin and guanosin. The two pyrimidin nucleotids are not further decomposed. Extracts of intestinal mucosa form mononucleotids and then convert the pyrimidin as well as the purin mononucleotids into the corresponding nucleosids. The purin nucleosids are broken down into d-ribose and purin bases. The pyrimidin nucleosids are not further changed. In fact they are apparently not decomposed by any tissue extract (Levene and La Forge). Plasmata of kidney, heart, muscle and liver have the same effect in decomposing nucleic acid as intestinal mucosa. Pancreas plasma, blood serum, and hemolyzed blood convert tetranucleotid into mononucleotids, but here the process stops.

The ferment that converts tetranucleotid into its constituent mononucleotids is called "nuclease." The four mononucleotids are broken down into mononucleosids by specific ferments called "nucleotidases." The conversion of nucleosids into their component base and carbohydrate is brought about by a third type of ferment called "nucleosidase."

Jones(*c*)(1920) found an active agent in the pig's pancreas not destroyed by heating which decomposes yeast nucleic acid into its mononucleotids. It is not present in the other organs.

Probably nucleic acid is not broken down in the intestine into the purin bases, but that the mononucelotids or nucleosids are absorbed as such and take a part in the intermediary metabolism (Thannhauser and Czoniczer). Bacteria in the intestine reduce nucleosids to ammonia, thus

splitting the purin ring. Ferments of the digestive glands do not have this action. It is probable that the source of the increased output of urea that follows the administration of nucleic acid is due to the bacterial purinolysis in the intestine.

The two nucleosids, adenosin and guanosin, injected subcutaneously or intravenously in normal man lead to an increased output of uric acid. The increase of the purin nitrogen in the urine accounts in some cases for nearly all the purin nitrogen introduced into the body in the form of a nucleosid (Thannhauser, Gudzent).

The amino-nucleosids, guanosin and adenosin, may undergo deamination forming the two oxy-nucleosids, xanthosin and inosin. The ferments involved are guanosin-deaminase (Jones(*b*)), and adenosin-deaminase (Amberg and Jones(*a*)).

Guanosin can form guanin by means of guanosin-hydrolase (Jones and Belt) and adenosin be changed to adenin by adenosin-hydrolase (Amberg and Jones(*b*)). Similarly xanthosin is converted into xanthin by hydrolysis (Jones), and inosin into hypoxanthin (Amberg and Jones(*a*), Levene and Medigreceanu(*b*)).

Xanthin and hypoxanthin are oxidized to uric acid by the ferment xanthin oxidase (Spitzer, Wiener). This is found in man in the liver only.

The two aminopurins, guanin and adenin, are converted into xanthin and hypoxanthin by the two separate ferments guanase and adenase, the existence of which has been proved by Jones and his associates, Partridge and Winternitz. Schittenhelm for years contended there was a single deaminase that changed the aminopurins into oxypurins. Jones(*a*), however, showed that the organs of different animals differ in the deaminases they contain. For example, the ox-spleen contains both guanase and adenase as Schittenhelm found, but pig's spleen contains adenase, but not guanase. Adenase does not occur in any human organ. Guanase is present in the kidney, liver and lung. While free adenin cannot be acted upon by human tissues, combined adenin, i. e., adenosin can be deaminized into inosin.

Uric acid is apparently the end product of purin metabolism in man and the ape (Wiechowski(*a*)(*c*)), but in lower animals it is oxidized to allantoin by the ferment uricase (Stockvis(*a*), Wiener, Wiechowski(*b*)), which has never been found in the human organism. Early experiments seemed to show that uric acid injected subcutaneously was excreted quantitatively. These results formed the chief support of those who claimed that uric acid was not destroyed in man. Recent studies have reopened this question which seemed definitely answered, and it is now known that a considerable part of uric acid injected intravenously is often not excreted in the urine (Bass(*b*), McClure and Pratt, Griesbach, Bürger). In one of my non-gouty cases only 22 per cent was eliminated. In Bürger's series the average output was only 52 per cent and the remainder retained in the

tissues is possibly destroyed. At any rate those that hold the view that uricolysis does not occur cannot support it now as formerly by the results obtained by introducing uric acid parenterally. Furthermore, Bornstein and Griesbach(*a*) show that the uric acid in the blood often decreases if kept at body temperature in sterile flasks for a few hours after its withdrawal from the body. Taking the evidence at present available it seems to the writer that while uricolysis probably does not occur in the human body, its existence has not been disproved.

Before concluding this section on the formation of uric acid from nucleic acid mention should be made of the fundamental observations upon which present knowledge is based. Horbaczewski(*a*) was the first to bring experimental proof of the formation of purin bases and uric acid from nucleic acid. By digesting the ox spleen, rich in nucleic acid in the form of nucleoproteins, with blood he obtained uric acid when oxygen was conducted through the mixture of spleen pulp, and xanthin and hypoxanthin when air was not introduced. He had no conception of the true nature of this formation of uric acid from the purin bases, but thought it was due to putrefaction. Wiener and also Spitzer proved that both xanthin and hypoxanthin are oxidized to uric acid by ferment action and Spitzer also discovered that xanthin-oxidase is confined to the liver and spleen.

Synthesis of Nucleic Acid and Uric Acid

Miescher who had discovered nuclein in his chemical study of pus cells found that the head of the spermatozoa of the Rhine salmon was free from protein and consisted of the same chemical body he had found in pus. It gave the reactions for protein, but contained phosphorus and was resistant to gastric digestion. This was nuclein. In ascending the Rhine the fish took no food. Spermatic fluid made up of spermatozoa in dilute salt solution is formed in great quantity at the expense of the muscle protein. This was a clear demonstration of the formation of nucleic acid from protein. Synthesis of nucleic acid from protein has been shown to occur in the developing hen's egg (Kossel), in young rabbits (Burian and Schur(*a*)), and in the adult Dalmatian dog (S. R. Benedict(*b*)). It is quite likely that the amino-acids arginin and histidin may serve as purin precursors (Ackroyd and Hopkins). The synthesis of uric acid from ammonium lactate and urea occurs in birds according to Minkowski(*b*). Kowalewski and Salaskin presented evidence that ammonium lactate was converted into uric acid by perfusion through an isolated goose liver. This work has been generally accepted, but Friedmann and Mandel and also Glaeserow maintain that convincing proof is lacking that ammonium lactate is converted into uric acid in the liver of birds. Many attempts have been made to prove the synthetic formation of uric acid in mammals.

Ascoli and Izar claim that they have experimental evidence that synthesis occurs, but their work has been refuted by Spiers and Wells. Synthesis of nucleic acid occurs in mammals, but synthesis of uric acid is not only unproved, but its existence is unlikely. Hence in the building up of the purin molecule in the body the process probably does not pass through a uric acid stage, but occurs in some way yet unknown.

The Source of Uric Acid in the Urine

With a person on a purin free diet the uric acid in the urine must come from his own tissues, either from broken down cell nuclei or from living cells as a product of nuclear metabolism. In any case the uric acid is endogenous in origin. For many years it was generally held that this output of endogenous uric acid was constant for the individual. Burian and Schur(*b*) and Sivén announced simultaneously in 1900 that with the individual on a purin free diet there was very little fluctuation from day to day in the uric acid excretion. Their observations were confirmed among others by Kaufmann and Mohr in Germany, Hall(*a*) in England, and in this country by Rockwood, and MacLeod and Haskins. This conclusion that the output of uric acid was constant was drawn from the study of too few individuals and has been found to be erroneous. It is now known that the character and quantity of the purin-free diet may influence greatly the output of uric acid. Folin(*c*) found that on a cream and starch diet about one-half as much uric acid was excreted as on purin free milk and egg diet and his observations were confirmed by Jackson and Blackfan. Leathes(*a*) also found that on a low protein diet the uric acid excretion is less than on a more normal one.

While in some individuals the output of uric acid is remarkably constant on a purin free diet, in others fluctuations amounting to 15 per cent or 20 per cent occur. Ackroyd(*a*) states that a fluctuation as great as 0.11 gram of uric acid is not abnormal. Examinations of the literature show wider variations than this in normal subjects. In Mallory's(*a*) normal case the maximum fluctuation in a period of 34 days was 0.20 gram, and a subject studied by Mendel, Underhill and White exhibited a variation of 0.19 gram in four days on a purin free diet.

Höst(*a*) in a recent study of 17 normal subjects found that with a fixed non-protein diet the uric acid output in a few subjects was constant, while in the majority it was irregular and showed variations from day to day up to 80 per cent. If the caloric value is increased or decreased considerably the uric acid output is always changed in the same direction. The change of uric acid output is greater when the amount of calories is varied by means of protein than by nitrogen free food elements. If the calories are kept constant, but the food protein changed beyond a certain minimum

there is always a corresponding change in the uric acid excretion (Höst). Lichtwitz(*l*) found this to be true, but his subject had difficulty in taking the large amount of protein given and this produced only a slight increase in the uric acid output. Individuals on a purin free diet usually excrete between 0.3 gram and 0.6 gram daily. In the fasting state, 12 to 15 hours after the last meal the excretion of uric acid sinks to a lower level than it does when the patient is taking a purin free diet. This is the "Nuchterwert" of Mareš(*a*), the "Hungerstand" of Burian. Mareš believes the uric acid output is constant for each individual, but only in the fasting state. Faustka in 1914 brought support for this view by re-examining the subject Mareš had studied in 1886 and finding the uric acid fasting value was unchanged.

The excretion of uric acid is less during the night than during the day (Rockwood, Hirschstein(*b*), Leathes(*a*)), and the hourly variations in the output are often considerable. The curve of elimination is characteristic and Pfeil found it alike in different healthy individuals. I have noted considerable variation in different subjects I have studied and also in the observations published by different writers. The output is greatest in the early hours of the day, that is before noon. Leathes found the maximum excretion between 10 A. M. and 1 P. M. Höst(*a*) in the first half of the forenoon. In a fasting subject under my observation the greatest hourly output was between 7 and 8 A. M. There is no doubt that the minimum excretion is at night. This is probably due to diminished renal activity at night (Hirschstein(*b*)), as the uric acid in the blood exhibits no corresponding fluctuations, but possibly to lessened formation of uric acid (Leathes(*a*), Cathcart, Kennaway, and Leathes).

The variations in the hourly elimination of uric acid which occur in the fasting individual during the day are due to unknown causes (Neuwirth).

The Effect of Purin-containing Food on the Output of Uric Acid.—Ingestion of food rich in nucleic acid is followed by an increased excretion of uric acid. This was first clearly shown by Weintraud(*a*), who observed a uric acid output of 2.5 grams after the feeding of a large quantity of calf thymus (750-1000 grams). Minkowski(*e*) fed hypoxanthin to men and found that it gave rise to a marked increase in the excretion of uric acid. These observations confirmed by many other workers seemed to prove that the nucleic acid of hypoxanthin and thymus was converted directly into uric acid which was promptly excreted by the kidneys. The uric acid supposedly formed from purins of the food is called the exogenous uric acid while that excreted on a purin-free diet is the endogenous (Burian and Schur(*d*)). It was maintained that a definite portion, about 50 per cent of purin nitrogen of the food, would be excreted as uric acid nitrogen in the urine of a healthy man. It is now known that no constant percentage of a purin substance contained in the food reappears in the urine as

exogenous purin nitrogen. It may vary in normal persons from 8 to 74 per cent (McClure and Pratt). When hypoxanthin was the purin substance administered, Ackroyd(*a*) found the percentage varied from 21 to 72 per cent, and the same individual gave different results on different occasions. Even when a very large amount of purin nitrogen is given in the food the uric acid output in any one day is rarely above 1.5 grams and is usually below 1 gram. If the purins of the food are directly excreted in the form of uric acid it seems remarkable that the feeding of very large quantities of purins produces such a relatively slight increase in the output of uric acid.

Mares(*a*) found an increase of the uric acid excretion during the first hour after meat was given to a fasting subject. The output reached its maximum during the fifth hour and then gradually sank. The increase of the urea began in the third hour after the ingestion of meat. Mareš(*a*)(*b*)(*c*) advanced the view that the increased output of uric acid after eating purin-containing food was due chiefly to the activity of the digestive organs. The fact that meat produces a more marked increase of uric acid output than purin-free albumin Mareš attributes to the greater stimulation of the digestive glands by the purin. It is a proved fact that albumin, free from purin, increases the uric acid excretion (Mareš, Mendel and Brown, Mendel and Stehle, Höst(*a*), Lichtwitz(*l*), Maurel, Taylor and Rose). Mareš regards this as evidence that the increased amount of uric acid excreted during the first few hours after the ingestion of meat does not come from the purins of the meat. The administration of carbohydrates also produces an increased output of uric acid, and this supports Mareš theory. Smetanka found that the slight increase which followed the ingestion of honey was greater than that caused by starch. It is evident that starch would call forth greater demands on the digestive organs, and Smetanka attributed the greater output caused by honey to stimulation of the glycogenic function of the liver. This is certainly a modification of Mares theory.

That the exogenous and endogenous uric acid formation cannot be sharply separated seems evident, but that the so-called exogenous uric acid is largely produced by the activity of the digestive glands seems doubtful. The secretions poured into the intestine contain purin bases, but even if all were absorbed unchanged this would account for but a small part of the uric acid output (Brugsch and Schittenhelm(*d*)).

If Mareš theory were correct it would seem to follow that in starvation the uric acid excretion would fall to a very low level as the activity of the digestive organs is at a minimum. There is always a marked drop in the uric acid during the first few days of a fast. A marked fall on the second day was observed by Schreiber and Waldvogel, F. Benedict and others, but there is a rise as fasting progresses (Cathcart(*c*)). During Benedict's study of a fast of thirty-one days, there were many days when

the uric acid was as high as one finds in a normal person on a purin free diet.

It has been shown that the ingestion of amino-acids increases the endogenous uric acid output. As no digestive activity is necessary for their utilization the rise in uric acid cannot be attributed to the work of the digestive glands (Lewis, Dunn and Doisy). As amino-acids probably stimulate cellular activity to marked degree (Lusk(*b*)(*d*)), the rise of uric acid may be attributed to a direct stimulation of nuclear metabolism in the body by amino-acids or their catabolic products, and the rise in uric acid observed by Mareš occurring during the first hours of digestion may be attributed in the light of this work on amino-acids with as much reason to stimulation of cellular activity by products absorbed from stomach and intestine, as to the activity of the digestive organs.

Uric Acid in the Blood in Health.—A small amount of free uric acid is always found in the blood. In 1913 Folin and Denis(*c*) published an accurate colorimetric method for its determination. They found amounts of uric acid ranging from 0.7 to 3.7 mg. per 100 c.c. of blood; Myers and Fine(*a*) using Benedict's modification of Folin's method 1.0 to 2.0 mg.; Gettler and Baker in a series of thirty normal cases 1.0 to 3.5 mg.

According to the old, but still generally accepted, view the uric acid in the blood is in the form of monosodium urate. Pure uric acid is about twenty times more soluble in serum than is monosodium urate (Roberts(*b*), Bechhold and Ziegler(*a*)).

It is held by some that sodium urate in the blood is in colloid form (Schade(*b*)(*c*)(*a*) and Boden(*c*), Bechhold and Ziegler). Other investigators deny the existence of a colloid solution of uric acid or of the urates in the blood (Gudzent(*d*), Kohler(*a*), Lichtwitz(*g*)).

The plasma and blood corpuscles contain varying proportions of uric acid (Steinitz(*b*), Bornstein(*a*) and Griesbach(*a*)). Sometimes there is more uric acid found in the serum, sometimes more in the corpuscles. In only two cases examined by Bornstein and Griesbach(*a*) was the uric acid found exclusively in the corpuscles. The cause of this difference in distribution is unknown. Analogies are seen in the distribution of blood sugar Steep(*a*), Loeb(*b*)).

In ox blood S. Benedict(*a*) found the uric acid exclusively in the corpuscles while in chicken blood it is almost all in the serum.

In 1915 S. Benedict(*a*) discovered that uric acid in ox-blood exists chiefly in a combined form. In one specimen he found .56 mg. of uric acid. After boiling with HCl the same blood yielded 5.87 mg. of uric acid. Benedict has recently isolated this combined uric acid in a pure crystalline state. It is a nucleosid in which the carbohydrate is pentose, and hence, a decomposition product of plant nucleic acid.

Bornstein and Griesbach(*b*) have found combined uric acid in the majority of specimens of human blood they have examined. The amount

of combined uric acid was about fifty per cent of the total uric acid. The freeing of the uric acid was accomplished by Benedict's procedure of boiling the protein-free filtrate with hydrochloric acid.

Bass(*c*), and later Schiller and Wiener(*a*), found in human blood purin compounds, either nucleotids or nucleosids, which on hydrolysis yielded adenin. They are present in the serum, but especially in the red blood corpuscles. The whole blood according to Bass contains between 6 and 10 mg. of purin nitrogen in 100 c.c. of blood.

Schiller and Wiener(*b*) using Schittenhelm's method found the free purin bodies in the blood varied from 1.1 to 2.8 mg. in 100 c.c. of blood. The uric acid formed between 25 and 50 per cent of the free purin bodies in the blood.

Thannhauser and Czoniczer give the nucleotid nitrogen of the blood as varying in health between 2 and 3 mg. in 100 grams of serum. It was about twice the amount of the free purin nitrogen. It is evident from these studies that the combined purins are present in the blood in much larger quantity than is free uric acid.

Only slight variations have been observed in the amount of uric acid in the blood of the same normal person at different times when on a purin free diet. In four determinations made over a period of nearly two months the uric acid varied only from 2.3 mg. to 2.5 mg. (McLester). Höst(*a*) maintains that on a purin free diet the uric acid in the blood is constant for the normal individual.

Denis(*b*) has shown that in health a period of high purin feeding lasting 5 to 10 days increases the uric acid in the blood only slightly (0.1 to 0.2 mg. per 100 grams) and sometimes it remains the same as on a purin free diet.

Uric Acid in the Organs and Tissues.—The various tissues contain quantities of free uric acid comparable to that in the blood of the same person (Fine(*a*)). There is evidence that uric acid precursors are stored in the liver (Rosenberg(*a*)(*b*)). Puncture of Claude Bernard's sugar center in the brain produces in dogs a marked transitory increase in the output of allantoin, the end product of purin metabolism (Michaelis(*a*)). This experiment suggests that uric acid like sugar is stored in the liver and in a form that is readily available.

Free uric acid introduced into the blood speedily disappears from the circulation. This seemed probable from the observations of Bass(*b*) who found that the blood two hours after an injection of uric acid contained but little more uric acid (about 10 per cent of the uric acid injected) than was present in the blood normally. The normal was determined by an examination of the blood about ten days before or after the injection. The studies of McClure and Pratt clearly showed that uric acid leaves the blood soon after its injection. The amount of uric acid was determined at the time that 0.5 gram of uric acid with 1 gram of piperazin

was injected intravenously and again four hours later. In one instance the uric acid was less at the second examination (2.9 mg.) than it had been before the injection (3.5 mg.), and yet the output of uric acid in the urine had not increased. They attributed the disappearance of uric acid from the blood to its entrance into the body tissues. Van Slyke(*b*) had previously shown that amino-acids introduced into the blood quickly leave the blood and enter the muscles. Urea behaves similarly. Griesbach also found that injected uric acid quickly left the blood. In two examinations only 5 per cent of the uric acid was found fifteen minutes after the injection. It has recently been discovered that most of the uric acid leaves the blood within five minutes after being injected into the peripheral circulation (Bürger). In some instances it entirely disappears from the circulation in that short time (Russell and Pratt). The rapid passage of uric acid from the blood to the tissues is probably due to forces which attempt to establish an equilibrium in the concentrations of uric acid in the blood and tissues. Frey has discovered the existence of a mechanism which equalizes the concentration when sodium phosphate, sodium chlorid and other inorganic salts are injected intravenously.

Recent observations have shown definitely that uric acid injected intravenously is often in large part retained in health as well as in gout and in other diseases. McClure and Pratt injected uric acid and piperazin intravenously in five non-gouty cases and found that the uric acid excreted varied from 22 per cent to 82 per cent in four cases, while the output in the fifth case was 138 per cent. The output in one of Dohrn's cases was 59 per cent, in another 63 per cent. Frank and Bauch reported only 40 per cent in one case, and Bass 67 per cent. These results were strikingly different from those obtained by Umber and Retzlaff, who claimed that when uric acid was injected intravenously into non-gouty persons it was practically all excreted.

Recent studies have confirmed our findings. Bürger in 1920 found that the average excretion of uric acid in forty-eight hours following the injection of uric acid and piperazin was 52 per cent in 12 cases, on the day of injection only 29 per cent. Uric acid in supersaturated solution was excreted in less amount, the average being only 27 per cent of the injected 0.5 gram. As piperazin itself increases the output of uric acid (His(*e*), Abl, Dohrn, Ewald) the amount excreted after the injection of uric acid and piperazin is only in part due to the uric acid. Griesbach also found incomplete elimination of uric acid introduced intravenously.

The dogma of the quantitative excretion of parenterally introduced uric acid which has been held by all authorities has been definitely overthrown by the work here recorded. Earlier observations had formed the most important evidence against the destruction of uric acid in the human organism. The experiments of Soetbeer and Ibrahim with subcutaneously injected uric acid, and especially those of Umber and Retlaff

seemed to prove conclusively that uric acid could be recovered quantitatively after injection into man. The work of McClure and Pratt, Griesbach and Bürger, shows that much uric acid may be retained. Advocates of uricolysis could advance these recent observations in support of their theory with as much justice as their opponents did the old experiments of Soetbeer and Ibrahim, v. Benezúr and Umber.

The injection of uric acid may be followed by the excretion of more uric acid than has been injected. In one of Griesbach's cases this amounted to 218 per cent. The uric acid injected, as has been shown, leaves the blood and enters the tissue fluids, joining the reserves already stored there. This newly discovered fact makes improbable the sharp distinction that has been held between exogenous and endogenous uric acid. The injected uric acid accumulates in the tissues and by increasing the concentration in the tissue fluids favors the passage of uric acid back into the blood and its excretion by the kidneys, possibly it also stimulates nuclear metabolism. It is a remarkable fact that the complex nucleoproteins taken as food produce a more speedy rise in the uric acid output than does uric acid introduced directly into the blood stream.

Uric Acid in the Blood in Gout

Alfred B. Garrod(*b*) discovered that the blood of gouty persons contained as a rule more uric acid than that of healthy men. Garrod's first observations were made in the summer of 1847 and the following year after investigating several cases of gout with uniform results he published his findings in the Transactions of the Medico-Chirurgical Society. At that time he drew the conclusion that the "blood in gout always contains uric acid in the form of urate of soda, which salt can be obtained from it in crystalline state." Eleven years later he wrote that the only alteration he would be disposed to make in this statement would be to append the words "in abnormal quantities." Garrod even attempted a quantitative analysis and obtained from the first patient the equivalent of 5 mg. of uric acid per 100 grams of blood serum. Garrod's(*c*) work did not receive the recognition it deserved until after the discovery by Folin and Denis in 1913 of a simple colorimetric method for determining the amount of uric acid in the blood. "The general harmony of his conclusions with current views is surprising when one considers the methods which were then available. It has been suggested that he drew on his imagination for some of his results, but the correctness of his deductions and the quantitative data which he gives do not support this" (V. C. Myers).

G. Klemperer(*a*), Magnus-Levy, v. Jaksch and other German investigators attempted to estimate the amount of uric acid in the blood either by the ammoniacal silver method or the cupric bisulphite method for precipi-

tating uric acid. But to obtain even a qualitative test it was necessary to take more than 75 c.c. of blood. In the cases in which positive results were obtained by Brugsch and Schittenhelm(*a*) 100 to 200 c.c. of blood were removed by venesection. The quantitative methods employed by these earlier investigators would fail to reveal moderate amounts of uric acid (1 to 2 mg.) and yet would give too high figures if any uric acid at all were found (Folin and Denis(*c*)).

In 1912 Folin and Macallum called attention to the possibilities of the use of phosphotungstic acid in the colorimetric estimation of uric acid. This color reaction on which the method of Folin and Denis(*c*) was based is so delicate that one part of uric acid can be recognized in a million parts of water. Their method was published in January, 1913. They reported the blood analysis obtained in five cases of gout. The uric acid ranged from 3.5 mg. to 5.5 mg. per 100 grams of blood. The following May Pratt(*a*) reported before the Association of American Physicians analyses made in Folin's laboratory of the blood in 11 cases of gout. The detailed findings are given in the following table:

TABLE I

Milligrams of Uric Acid Per 100 Grams of Blood in Cases of Gout

Case	Patient	Age	Date of Examination	Ordinary Diet		Purin-free Diet		After administration of atophan in attack
				Attack	Interval	Attack	Interval	
I	A. B.	66	Oct. 15	....	5.5			
			Nov. 3	....	5.5	....	3.4	
II	E. T.	30	Nov. 9	....	3.5			
			Apr. 14	....	5.0			
III	J. K.	45	Nov. 12	....	4.4			
			Apr. 17	....	5.5			
IV	D. H.	45	Jan. 20	....	4.0			
V	D. N.	58	Mar. 21	....	....	3.1		
			Mar. 23	....	....	....	....	2.2
VI	J. H.	36	Mar. 27	5.7				
			Apr. 1	....	....	....	....	2.2
VII	G. K.	55	Mar. 27	....	....	2.4		
			Apr. 1	....	....	....	....	2.1
			Apr. 16	....	....	3.6		
			Apr. 21	....	....	5.1		
			Apr. 25	....	....	....	....	1.6
VIII	R. S.	45	Apr. 12	....	3.9			
IX	E. D.	61	Apr. 14	....	4.5			
			Apr. 21	....	....	....	....	1.2
X	J. U.	62	Apr. 14	....	3.9			
XI	W. L.	59	Apr. 24	....	3.1			

Benedict(*a*) in 1915 published a modification of Folin's method which materially simplified it. In 1919 Folin and Wu described a simpler and more accurate procedure for uric acid determinations.

Normally 1 to 3 mg. of uric acid are present per 100 grams of blood, but in gout 3 to 9 mg. are found. Low figures have been reported by my-

self and others in undoubted tophaceous gout, but they may have been due to errors in the original Folin method. In one of my patients 1.7 mg. of uric acid was found (purin-free diet). Nearly two years later at a second examination the still lower value of 1.3 mg. was obtained. The fact that the two lowest analyses were obtained in the same case with a long interval between the tests makes a technical error an improbable explanation of the low value. In another case on a mixed diet there was but 1.9 mg. Daniels and McCrudden also reported two cases of supposedly chronic gout with low normal values of uric acid in the blood. In their paper conclusive evidence of gout was not presented. The patients had not had typical podagra and tophi were not found.

A low normal amount has not been observed in gout since the new method has been employed, but as in relatively few cases have blood examinations been made with this method the question is still unsettled.

McLester (using Folin's original method) found uric acid in the blood of fifteen normal subjects who had been on a purin-free diet at least three days, in amounts ranging from 0.5 to 2.9 mg. per 100 gm. of blood with an average amount of 1.9 mg. In 156 non-gouty patients on a mixed diet the average value was found by Adler and Ragle to be 1.7 mg. In 16 cases of gout irrespective of diet I found the average amount to be 3.7 mg. In patients examined when on a purin-free diet the uric acid ranged from 1.6 to 7.2 mg. The largest amount I have observed was 8.7 mg. This was in the blood from a case of chronic gout with multiple tophi, two days after a sweetbread meal. Higher values than this have rarely been obtained, but Fine in one case of gout found 9.5 mg.

The blood during an acute attack usually contains more uric acid than at other times, but the increase is small, being rarely more than 1 mg. Bass and Herzberg have observed cases in which the uric acid did not increase during attacks.

In gout the uric acid in the blood is usually reduced somewhat by a purin-free diet, but the amount generally remains above the normal level. It may, however, fall to normal as shown in the following case in which the purin-poor diet had been taken for more than two years when the normal value was obtained.

Acute gout—many typical attacks. No tophi.

April 5, 1915.	Mixed diet	4.8 mg.
" 14, "	Purin-poor diet for 9 days	3.5 "
Jan. 26, 1916.	One week after onset of attack of gout which lasted three days	4.0 "
June 27, 1917.	Purin-poor diet for 2 years and 2 months	2.0 "
April 21, 1921.	Purin-poor diet for 6 years	2.4 "

Case 1 of my series A. B. was taking a small amount of meat or fish daily on Oct. 15, 1912, when the uric acid was found to be 5.5 mg. per 100 grams of blood. He was then placed on a purin-free diet. The blood on Nov. 3, 1912, contained 3.4 mg.—a drop of 2.1 mg. Sometimes the uric acid may increase in spite of a purin-free diet. The blood of T., a patient with gout, contained 5 mg. of uric acid on Aug. 6, 1915. On Sept. 16, 1915, although he had been on a purin-free diet a month, the uric acid had risen to 5.8 mg. The purin-free diet was continued and on Dec. 9, 1915, the uric acid had fallen to 4.2 mg.

Great fluctuation in the amount of uric acid in the blood independent of diet is sometimes observed in other diseases and was strikingly shown in a case of chronic non-gouty polyarthritis, as follows:

McC. aged twenty-two years.	Mgs. of uric acid per 100 gm. of blood.
October—Ordinary diet	2.7
December—Purin-free diet	5.0
May—Purin-free diet	1.6

In another case of chronic non-gouty arthritis the blood when first examined contained 7.6 mg. of uric acid. A few months later, when on a diet rich in purins, only 0.8 mg. was found.

There is sometimes a marked increase of the uric acid content of the blood in gout 1 to 3 days after feeding a single meal rich in nucleic acid, as shown in the following table.

TABLE II

	Mgs. of uric acid in 100 gms. of blood		Mgs. of uric acid in 100 gms. of blood
D. N. Gout. Purin-free diet	3.1	52 hours after eating 280 gms. haddock roe	5.8
		3 days after eating 300 gms. roast beef	6.2
K. Gout. Purin-free diet	2.4	24 hours after eating 270 gms. roast beef	3.0
H. Gout. Purin-free diet	1.7	3 days after eating 150 gms. thymus	3.6
P. Gout. Purin-free diet	2.1	3 days after eating 160 gms. thymus	3.4
J. N. Gout. Purin-free diet	2.2	48 hours after eating 190 gms. thymus	8.7
Average	2.2	Average	5.1

In four non-gouty persons the amount of uric acid in the blood was determined twenty to forty-eight hours after feeding a sweetbread meal. The results are given on the next page.

TABLE III

	Mgs. of uric acid in 100 gms. of blood		Mgs. of uric acid in 100 gms. of blood
McC. Chronic polyarthritis. Purin-free diet	1.7	24 hours after eating 100 gms. of thymus	2.2
R. Multiple recurrent thrombosis: streptococcus isolated from blood. Purin-free diet	2.0	48 hours after eating 300 gms. of thymus	2.3
M. Chronic polyarthritis. Ordinary diet	2.0	24 hours after eating 225 gms of thymus	1.8
H. Chronic polyarthritis. Ordinary diet	2.9	47 hours after eating 190 gms. of thymus	2.5
Average	2.1	Average	2.2

On comparing the figures given in the two tables it will be seen that prior to the sweetbread meal the average amount of uric acid present in the blood of the gouty and the non-gouty patients was practically the same. Twenty-four hours to three days after feeding the exogenous purin the average amount of uric acid was 5.1 mgs. in the blood of the gouty, while in the blood of those who did not have gout it was only 2.2 mgs.

Exogenous purins in five gouty patients produced marked hyperuricemia twenty-four hours to three days after they were fed, while in individuals who did not have gout the uric acid concentration was practically unchanged twenty-four to forty-eight hours after the purin meal.

These observations indicate that the uric acid derived from exogenous purin does not accumulate in the blood unless there is a disturbance in the uric acid metabolism. In one patient, however, who had recurrent iritis, but whose history and physical examination revealed no evidence of gout, the uric acid content of the blood was abnormally high two days after a sweetbread meal. His blood on November 1 after having been on a purin-free diet for two days contained 2.2 mgs. of uric acid. On November 7 he ate 150 grams of sweetbread. Two days later there was 4.8 mgs. of uric acid in the blood. With the sweetbread meal he took two cocktails. It is possible that the alcohol caused a transitory disturbance of the uric acid metabolism. Pollak has shown that a retarded and diminished excretion of exogenous purin may occur in chronic alcoholism. No persistent increase of uric acid existed in my patient as the blood examined on March 30 when on a mixed diet contained only 0.8 mg. of of uric acid. This is a lower amount than has been found in any case of gout.

The increase in the uric acid content of the blood in gout after feeding a purin meal may not appear for twenty-four hours or more, and an initial fall has been observed in two cases of gout in which the blood was examined four to eleven hours after the sweetbread meal.

After injecting 0.5 gram of uric acid with 1 gram of piperazin intravenously McClure and Pratt found in four gouty patients that uric acid was increased from 0.5 to 1.8 mg. four hours later. In three patients the increase persisted for forty-eight hours or longer. In four out of five non-gouty subjects there was a similar increase, but it disappeared in all of these within twenty-four hours. Retention of uric acid in the blood either when injected intravenously or when large amounts of nucleoproteins are fed, would seem to be a characteristic feature of the disturbed metabolism in gout.

A marked increase of uric acid in the blood has been repeatedly found in different types of chronic arthritis by different observers, but the hyperuricemia in my experience is not persistent as in gout. Folin and Denis(*h*) hold that in chronic non-gouty arthritis the other waste products represented in the non-protein nitrogen of the blood are not infrequently abnormally high, while in gout they are usually within normal limits.

In early chronic interstitial nephritis the uric acid is frequently as high as in gout while the urea nitrogen is slightly if at all increased (Myers and Fine(*c*)). Baumann found the uric acid increased in the blood in 74 out of 100 cases of renal involvement. In this group the maximum amount of uric acid found in cases with slight impairment of renal function was 6.4 mg., in cases with moderate disturbance of the kidneys 7.3 mg.

Much larger amounts of uric acid have been obtained in the terminal stages of chronic interstitial nephritis than are ever found in gout. The largest amount ever reported was 27 mg. in a case of uremia shortly before death (Myers and Fine(*b*)). In several cases of nephritis amounts as high as 15 mg. were observed by these investigators. High values do not occur in chronic parenchymatous nephritis (Myers). Uric acid in the blood is also increased in leukemia, but the large amount found in a case by Magnus-Levy(*i*) was probably in excess of the true value as the method used was inaccurate. It is also increased in lead poisoning and acute infections, especially lobar pneumonia and according to Gudzent, Wille and Keeser in many cases of old lues, tabes, paralysis, and tuberculosis studied by them.

The exact state in which uric acid circulates in the blood in gout is not known. Whether in normal blood uric acid occurs in the form of sodium monourate is undecided although that is the opinion of most authorities. Gudzent(*b*) holds that uric acid occurs in the blood as the easily soluble labile lactam urate which readily changes into the stable but poorly soluble lactim urate. It is possible that in gout the uric acid is chiefly in the latter state which would favor its deposition in the tissues. The colloidal properties of uric acid may have some relation to the pathology of gout. Uric acid and the urates tend to form supersaturated solutions. Before the uric acid changes from the clear solution to the solid crystalline form it passes according to Schade and Boden(*a*) through a colloid stage

and can under certain conditions be deposited as a homogeneous gelatinous substance.

The uric acid may occur in a form not demonstrable by Folin's method. It was shown by S. Benedict to exist in ox blood almost entirely in the combined form. Bornstein and Griesbach(*b*), using Benedict's method, found in the cases of human blood they examined that about 50 per cent of the uric acid was in a combined form. They examined only one case of gout and in this case there had been no attack for several years. The free uric acid was 1.84 mg., the combined uric acid 1.11 mg., making a total of 2.95 mg. per 100 c.c. of blood. Thannhauser and Czoniczer have shown that adenin and the nucleosids do not give the uric acid reaction with phosphotungstic acid until after boiling with mineral acid. These recent findings open up new lines of investigation, and it is possible that in gouty subjects the precursors of uric acid or combined uric acid are present in larger amount or in different proportions than in health.

Uric Acid in Joint Exudates in Gout

Garrod(*c*) noted the presence of uric acid suspended in the fluid from inflamed gouty joints. In its relation to the joints Friedrich Müller has called uric acid an arthrotropic substance. Bass and Herzberg attempted to measure the degree of arthrotropia by comparing the amount of uric acid in the joint fluids from gouty and non-gouty cases. The joint fluid was obtained by puncture, usually post mortem, and the uric acid determined in this as well as in the blood. Fluid from the knee joint was chiefly used in these tests. In five non-gouty cases with exudate into the joints the concentration of the uric acid in the joint fluid and in the blood was practically the same. Two cases of gout were examined. The values of the examinations was lessened by the fact that both patients had uremia.

		Uric acid concentration. Joint exudate	Uric acid concentration. Blood.
Case I.	Gout. Uremia	18.5	10.0
" II.	Chronic gout. Uremia	20.8	8.2

The much greater concentration of uric acid in fluid from the knee joints in gouty inflammations than in the blood suggests that determinations of the uric acid in joint exudates would be of diagnostic value. I have recently, however, examined the fluid from the knee in an undoubted case of chronic tophaceous gout during an acute attack located in the foot and knee. The blood contained 5 mg. of uric acid, but the clear fluid from the knee contained only 3 mg. A few months later the patient died.

At the autopsy the knee joint from which I had removed the fluid was found to have its lining membrane and the cartilage below coated with urates.

Uric Acid in the Tissues in Gout

Uric acid quickly leaves the blood when injected into a vein and enters into the tissues both in healthy persons and in gouty subjects. Whether it is deposited in especial situations, for example the liver, is not known. In two cases of uremia studied by Fine the distribution was fairly uniform. There was only slightly more in the liver than in other organs, and in one case more was found in pleural fluid than in the liver or blood. It is possible of course that the distribution might be different in gout, but no similar analyses in that disease have yet been made.

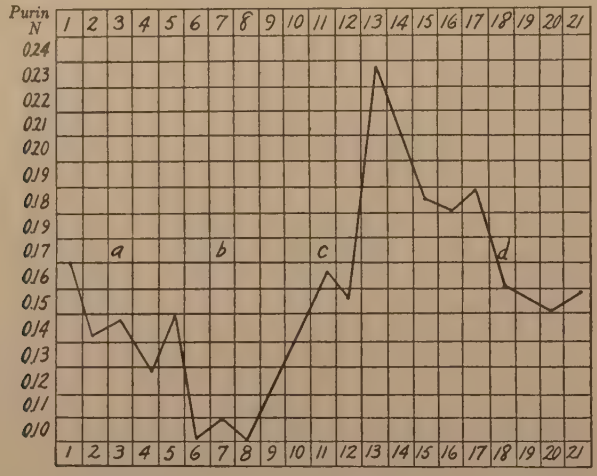
The drug atophan causes an increased excretion of uric acid by the kidneys, which usually exceeds in amount all the uric acid contained in the blood. Assuming that the blood volume is 1/13 of the body weight (Keith, Rowntree and Geraghty), a man weighing 65 kilos will have 5,000 gm. of blood. If the blood contains 2 mg. uric acid per 100 grams of blood, which is an average amount in health, there would be a total of 100 mg. in all the blood. In a gouty person of this weight a concentration of 5 mg. uric acid per 100 grams of blood would equal 250 mg. in the whole blood. In the first twenty-four hours after the administration of atophan is begun gouty patients frequently excrete an amount of uric acid above the endogenous level in excess of 250 mg. In a case studied by Graham the extra uric acid excreted during three days was 840 mg. During this time the loss of uric acid in the blood was only 64 mg. The extra uric acid excreted was more than ten times that lost by the blood and this extra amount must have come from the tissues. The water of the body constitutes 90 per cent of its weight and if this holds the same percentage amount of uric acid in solution as the blood, as is indicated by Fine's analyses, there is a considerable amount of uric acid in the body. On this assumption Graham calculated that the uric acid in the body fluids of his patient, weight 51.5 kilos, was 2.11 grams before and 1.36 grams after the atophan. That is a diminution of 0.75 gram, which corresponds fairly well to the extra excretion in the urine during the three days, which was 0.84 gram.

In cases of gout under the influence of atophan the increase of uric acid above the previous level persists usually much longer than in health. Bauch gave a patient with gout 3 grams of atophan daily for thirteen days. During this time he excreted 3 grams of uric acid above the endogenous value. In the normal individual the increased output ceases usually in a day or two in spite of continued administration of the drug.

The Urine in Gout

For a day or two previous to the onset of an attack of acute gout the amount of uric acid in the urine falls. This drop is followed by a marked rise reaching the maximum on the second or third day of the seizure. The output again lessens as the attack abates, but does not usually reach the low level of excretion that preceded the attack.

This characteristic curve of the uric acid output has been observed and described by many investigators and occurs when the patient is on an ordinary diet as well as on one that is purin free. The variations in excretion are well shown in the accompanying chart taken from Umber and in the chart that Osler gives in his text-book from a case studied by Futcher in his wards.



Daily Output of purin nitrogen in the urine of a gouty subject on a purin-free diet (Umber). *a*, *d*, Stage of depression in excretion following an acute attack of gout; *b*, depression stage preceding an attack; *c*, onset of attack.

On a mixed diet the output of uric acid in the intervals between attacks is not abnormally low (His(*e*)). The endogenous uric acid output in gout is low in the majority of cases. According to Schittenhelm and Schmidt (*b*) it is below normal in 80 per cent of the cases. From analyses collected from the literature, I found that the average daily excretion of twenty normal persons on a purin-free diet was 0.39 gram, while the average daily excretion of twenty gouty persons was 0.25 gram. In some cases of gout very low figures have been obtained. In Pollak's(*a*) case the average endogenous excretion over a period of five days was 0.06 gram. In a case of gout with a history of lead poisoning reported by Eschenberg the excretion was as low as 0.02 to 0.04 gm. In one of my own cases the output was 0.07 gm. for two successive days, but rose to 0.33 gm. three days later.

Futcher has observed a case in which the excretion was nil for twenty-four hours. His analyses were made a good many years ago, and probably with present-day methods some uric acid would have been found. Low values occur most often when gout is associated with plumbism (Mallory).

Soetbeer studied the hourly excretion of uric acid in gout and found that it deviated from the normal, both in chronic and acute cases. His curves show extreme irregularity of form. Sometimes the early morning rise in uric acid excretion which is a constant feature in health was missing. This is not diagnostic, however, as I have seen it absent in non-gouty cases.

The following table gives the hourly output in a case of tophaceous gout toward the end of an attack. The output on that day, 0.03 gram it will be noted, was very low, in fact one of the lowest ever recorded.

	Amount of Urine	Uric Acid	Mg. per Hour
Feb. 2-3			
7 P.M.—7 A.M.	400	0.010 g.	0.8
9 A.M.	37	.0028 g.	1.4
11 A.M.	50	.0065 g.	3.25
1 P.M.	50	.0026 g.	1.3
3 P.M.	65	Trace	—
5 P.M.	50	"	—
7 P.M.	55	.005 g.	2.5
9 P.M.	47	.005 g.	2.5
Feb. 3-4			
9 P.M.—7 A.M.	600	.015 g.	1.5

In some cases of gout the endogenous uric acid level is a high normal. Brugsch states that this most commonly occurs in chronic polyarticular gout, and my experience supports this view.

In gout exogenous purin is excreted less well than in health. McClure and Pratt collected 50 observations from the literature. In 32 of these 20 per cent or less of the purin nitrogen of the food was excreted as uric acid nitrogen. In 19 tests the excretion of exogenous uric acid was 10 per cent or less. These results are strikingly different from those obtained in health. Among 40 observations on healthy subjects in only 3 was the percentage of exogenous uric acid 20 per cent or less. In these studies the form in which the nucleic acid precursors were fed made little difference.

Hypoxanthin, which by simple oxidation produces uric acid, causes no greater percentage output of uric acid than nucleoprotein, although the latter requires the action of a series of ferments before its conversion into uric acid.

The intravenous injection of 0.5 gram of uric acid has been made in

a number of cases of gout (Umber and Retzlaff, Bürger and Schweriner, McClure and Pratt). In two of our four cases no increased excretion resulted and in one case in each of the two previous investigations none of the uric acid was excreted. In one of our patients the increase over the endogenous level was 44 per cent. This is more than may occur in healthy subjects. One of our patients with non-gouty arthritis excreted only 22 per cent. Injections of uric acid made during an attack of gout are more apt to be retained than when the test is made in the intervals between attacks. This is also true when purin substances are fed.

The diminished excretion of exogenous uric acid in gout is of little value in diagnosis as it occurs in many cases of chronic arthritis. Out of 52 tests on 41 cases of non-gouty arthritis in 17 twenty per cent or less of the purin nitrogen fed was excreted in the urine (McClure and Pratt). A diminished excretion also occurs in some cases of chronic alcoholism (Pollak) and probably in other conditions.

Brugsch and Schittenhelm(*b*) maintained that in gout there was a delayed as well as a diminished excretion of exogenous uric acid. This view has been widely accepted. In health, however, the excretion often extends over two or three days. Of fifty-two experiments on arthritic patients, the exogenous uric acid output was completed within five days in forty-one, or 79 per cent; and of forty-six experiments on gouty persons the output was ended within five days in forty-one or 90 per cent. Therefore, a prolongation of the excretion of exogenous uric acid is not peculiar to gout (McClure and Pratt).

Levene, Kristeller and Manson observed that after the administration of very simple nitrogenous substances such as urea and aspargin in a case of tophaceous deforming gout, the surplus nitrogen was not excreted in the same manner as in a normal individual, or as in a patient with chronic interstitial nephritis who was placed on a low nitrogen intake. In the case of gout the increase in the nitrogen output was comparatively low during the first twenty-four hours and the slightly increased excretion usually continued for several days. Levene and Kristeller(*b*) later found that the removal of nitrogen taken in the form of nucleic acid derivatives lagged behind the nitrogen output after the administration of urea. The nearest to urea in its action was inosin, then followed nucleic acid and hypoxanthin. The smallest increase in the nitrogen output followed the ingestion of uric acid and guanosin, possibly owing to the comparative insolubility of these substances. There was better elimination when the standard diet contained 13 grams of nitrogen than on one containing only 7 grams.

Action of Phenylcinchoninic Acid (Atophan, Cinchophen) in Gout.—In health atophan (cinchophen) produces a marked increase in the output of uric acid in a subject on a purin-free diet. This increase may begin within forty-five minutes. It persists one or two days and is followed by a fall below the original level in spite of the continued administration

of the drug. In gout the increased output may continue for many days. The uric acid in the blood drops markedly within a few hours (Folin and Lyman, McLester, Fine and Chace(*d*), Smith and Hawk).

Griesbach and Samson claim that this fall is preceded in some cases at least by a transitory increase of the blood uric acid. It is probable that atophan exerts an elective stimulation on the kidneys which increases the secretion of uric acid (Weintraud(*c*)). In addition to its stimulating action on uric acid excretion it appears to have an inhibitory action on the whole purin metabolism (Starkenstein(*c*)). Haskins(*c*) has noted periods of depressed output when the administration of atophan had been discontinued. There is no evidence that it causes an increased nucleic acid metabolism as Nicolaier and Dohrn held. Atophan, either acting directly or as a result of its renal action in removing uric acid from the body, mobilizes the uric acid in the tissues and organs. In this way a new supply continues to enter the blood. The increased output of uric acid in gout induced by atophan comes from reserves in the body (Frank and Przedorski, Starkenstein(*c*), Rosenberg, Graham). This action of the drug is strong evidence that the uric acid in gout is retained in the tissue fluids in considerable amount.

When uric acid is injected into the veins or when sodium nucleate is fed in most cases of gout the uric acid is largely or entirely retained in the body, but under the influence of atophan in these cases the exogenous uric acid is quantitatively excreted (Frank and Bauch).

Deposition of Sodium Monourate in Gout.—The most characteristic feature of gout is the deposition of sodium monourate in the tissues. It is this alone which sets it apart as a clinical and pathological entity from other forms of arthritis. In acute attacks of gout it has been held since the time of Garrod that uric acid is always deposited in the acutely inflamed tissues. In chronic gout collections of sodium monourate are found in sites of predilection—cartilages, especially of the metatarso-phalangeal joint of the great toe, the finger joints, and of the ear; fibrous capsules of the smaller joints of the hands and feet; bones of the fingers; prepatellar and olecranon bursas; and subcutaneous connective tissue. In subacute localized inflammations of the subcutaneous tissues (gouty abscesses) and of the bursas the contents in the early stages consist of a milky fluid containing prisms of sodium monourate. Later the fluid disappears and chalky concretions remain. These consist chiefly of sodium monourate, but may contain a small amount of lime.

The local conditions that cause the deposition of urates is unknown as well as the relation of the urates to the acute inflammation. The blood in gout is not supersaturated. It will dissolve uric acid in considerable amount (Klemperer(*a*)). But even if the blood were supersaturated that fact would not explain the deposit of uric acid in the tissues. It is quite possible that the amount of uric acid in the tissue-fluids may exceed the

saturation point as a result of local changes. The experiments of Almagia and Brugsch and Citron show that uric acid may be deposited in cartilage placed in weak uric acid solutions. This is possibly due to the richness of cartilage in sodium. If the more soluble lactam form of sodium urate were changed in the tissues to the much less soluble lactim salt its deposition would be favored. Histogenetic influence might interfere with the formation of Schade's uric acid-colloid phase and thus favor the precipitation of uric acid (Umber). But this subject is too hypothetical to deserve further discussion. The injection of urates into the tissues produces inflammation and necrosis (Freudweiler(*a*)(*b*), His(*a*)(*c*)).

The acute local symptoms in gout are most probably due to the deposition of crystalline urates which has been shown by Van Loghem to produce an inflammatory reaction.

The intramuscular injection of 0.5 gram uric acid dissolved in piperazin produced in a gouty subject much more severe reactions than have been observed in healthy persons (Brugsch and Schittenhelm(*g*)). Uric acid introduced intravenously, however, does not produce symptoms either in gouty or in healthy individuals. Nucleosids when injected subcutaneously have produced typical attacks (Thannhauser) and so has nucleic acid when fed in the form of nucleoproteins. These recent observations with nucleosids suggest that these precursors of uric acid rather than uric acid itself are the toxic substances in gout.

General Metabolism in Gout.—The general metabolism in gout is not altered (Magnus-Levy(*d*), Wentworth and McClure). In attacks there is an increase in the nitrogen metabolism due to toxic nitrogenous catabolism (Magnus-Levy(*d*), Brugsch(*b*)). Between the attacks the nitrogenous metabolism which von Noorden thought subject to disturbances of toxic origin has been definitely shown by Brugsch and Schittenhelm to be normal.

Glycocoll in Gout.—The part that glycocoll might play in the origin of gout has attracted considerable attention. Uric acid by hydrolysis is converted into glycocoll and urea. Ignatowski(*b*) found glycocoll in the urine of seven gouty patients. This was confirmed by Lipstein and Walker Hall(*b*). But the finding was apparently robbed of any significance in gout by the discovery that it occurred in equal amounts in the urine of normal persons (Abderhalden and Schittenhelm(*c*), Samuely (*b*)).

Umber still asserts that the glycocoll found in normal urine is not preformed, but is the result of the long continued action of alkalies on the uric acid in the chemical analysis. It is claimed by Umber and his coworkers, Hirschstein(*a*), Bürger and Schweriner, that in gout an antagonism exists between the excretion of uric acid and glycocoll. During the period of uric acid retention the glycocoll excretion is high, while during the period of "uric acid flood" in the attack it may entirely cease. Umber

considers this relation in the excretion of uric acid and glycocoll to be pathognomonic of gout.

Bürger and Schweriner claim that the intravenous injection of uric acid in gouty subjects about doubled the output of glycocoll while the uric acid was largely retained. This same procedure in health led to no excretion of glycocoll. The value of all this work is impaired from the fact that there is no direct method for determining glycocoll and the indirect methods are not reliable (Samuely(*c*), Abderhalden and Guggenheim(*b*)).

Kionka's(*a*) theory that in gout glycocoll is not completely burned and Frey's claim that uric acid could be destroyed and glycocoll formed in the blood have been rejected (Abderhalden and Schittenhelm(*c*), Brugsch and Schittenhelm(*c*)). Kionka's(*b*) experiment of adding uric acid to blood and finding glycocoll proved nothing because the uric acid was recovered unchanged.

Theories of Gout

The Renal Theory.—This was advanced by Garrod the elder in 1848, and has many adherents to-day. According to this theory gout is primarily a disease of the kidney and not a metabolic disorder, "at least in so far as the uric acid phenomena of the disease are concerned" (A. E. Garrod (*e*)). In early interstitial nephritis there is evidence of uric acid retention, as the concentration in the blood often exceeds that in gout (Fine and Chace). McClure found "definite depression" of renal function in all five cases of gout he tested by modern methods. The disturbance in renal function was slight in most of these cases. There is certainly no definite relation between the degree of nephritis present and the retention of uric acid. This was shown in the cases studied by McClure and Pratt. The patient with most severe nephritis, and whose phthalein output was only 5 per cent in two hours, excreted the largest percentage of exogenous uric acid of any in our series. On the other hand in a case in which all the uric acid injected was retained, there was no albumin or casts in the urine, and the phthalein excretion was 52 per cent.

The low endogenous level of uric acid output in gout in the intervals between attacks with the high uric acid concentration in the blood suggests that the kidneys excrete uric acid with difficulty in this disease. This idea of functional impairment of the kidney is weakened by the fact that during the height of an acute attack they frequently put out an abnormally large amount of uric acid.

If the high blood uric acid in chronic interstitial nephritis indicates its relation to gout, a "potential gout" as it were, it is remarkable that the retention of uric acid in chronic interstitial nephritis is so rarely followed by symptoms of gout.

The accumulation of uric acid in the blood probably favors the deposi-

tion of urates, but it is certain that not every excess of uric acid in the blood leads to a deposition of urates. It is also certain that in gout local changes in the places where tophi are formed play an important part.

The Ferment Theory.—Brugsch and Schittenhelm held that gout was an anomaly of the entire system of ferments concerned in the formation and destruction of uric acid. In gout, according to them, there were retarded uric acid formation, retarded uric acid destruction, and finally retarded uric acid elimination. The correctness of the elaborate theory they built up was made improbable by Wiechowski, who found that uric acid was not destroyed by any human organ, and by Jones and his coworkers who demonstrated that the distribution of ferments in gout was not different from that in normal persons.

The Combined Uric Acid Theory.—Minkowski in 1900 pointed out that proof was lacking that uric acid circulating in the blood and tissue juice was in the form of a simple alkali salt. He suggested that in gout uric acid might be in a form not readily excreted. This view he based on some experiments in which uric acid was combined with nucleic acid and thereby changed so that it could not be precipitated from the solution by the addition of acetic acid or by silver and magnesia in ammoniacal solution. Dohrn made this hypothesis more definite by advancing the view that in the blood of gouty subjects a nucleotid circulates whose purin portion was already oxidized to uric acid. This idea of a combined uric acid in gout finds some support from the discovery by S. Benedict of a uric acid nucleosid in ox blood.

Tissue Retention Theory.—According to Umber(*g*) the tissues in gout have a special affinity for uric acid. There must be an abnormal chemical property of the tissues which leads to this retention. He holds there are present an increase of receptors for uric acid which the normal tissues possess in less number and that the same mechanism exists for the retention of the arthrotropic poisons of metabolism in other joint diseases; for example, homogentisic acid which injures the joints in ochronosis.

Recent studies made with atophan and the result of intravenous injections of uric acid show that in gout uric acid is retained in the tissue juices in considerable amount and thus give support for the hypothesis that there is a special affinity of the tissues for uric acid in this disease.

Treatment

It would seem that the clinical experience of the best observers since the time of Sydenham would have settled long ago the question as to the proper diet in chronic gout, but it did not do so. All authoritative writers were agreed that the diet formed the most important part of treatment, but their ideas as to what constituted the proper diet differed widely. Sydenham himself emphasized the importance of moderation in meat and

drink. Wollaston over a century ago advocated the exclusion of all flesh food. Sir Alfred Garrod(*d*)(1859) advised careful restriction as to quantity of meat, but stated also that experience has clearly shown that gout cannot be successfully treated by abstinence from meat. Luff, writing in 1907, stated that "animal food, at all events in moderate quantity, was distinctly indicated" in chronic gout. In a few intractable cases of chronic gout it may be found necessary, he said, to reduce the diet to lean meat and water, the so-called "Salisbury diet." Sir Clifford Allbutt(*b*) said in 1921 that "it is popularly asserted in England at the present time that the gouty do well on this diet." Roberts and Rose Bradford, in Allbutt's System, stated that gouty persons should be advised to "partake cautiously of butcher's meat, fowl and game." Futcher(*b*), writing in Osler's System, would allow meat in moderate amounts. "It is often advisable," he adds, "from time to time to limit the meats to one meal a day." Minkowski(*i*) held a similar view.

Within the past twelve years there has been greater unanimity of opinion and the tendency has been distinctly toward a purin-poor diet. Von Noorden(*n*), Umber(*f*), Brugsch and Schittenhelm(*e*) all emphasized the importance not only of a meat-free diet, but one in which the purins are reduced to the lowest possible amount. The two English authors of recent books on gout—Lindsay (1913) and Llewellyn (1920)—still adhere to the view that meat in moderation is indicated in chronic gout. It is interesting to compare the views of the writers on gout in the three different systems of medicine that have just been published in America. McPhedran in Tice's System (1920) holds to a low caloric diet, but would not interdict wholly the use of meat. Pratt (1920) in Nelson's System advocates a purin poor diet free from all meat, and Allbutt (1921) in the Oxford System advises strict moderation "of meat, never more than the content of a neck chop should be taken" and in a mild case this quantity or its equivalent in fish five days a week, in severer cases every other day or twice a week and in obstinate cases "meat may have to be altogether barred, and even fish taken sparingly."

Minkowski(*l*)(1913) in his latest publication favored more strongly a purin poor diet than in his earlier writings. Archibald Garrod (1913) advocated the limitation, but not the exclusion, of purins from the food. His fear that harm might result if the rebuilding of the nucleoproteins was not facilitated by providing some purin substances in the diet seems unwarranted. In the first place it is impossible to give a patient a purin free diet. Vegetables contain not inconsiderable amounts of purin, and Voegtlin and Sherwin (1918) found in cow's milk more than traces of guanin and adenin. Furthermore, there is no doubt that nucleic acid may be formed from protein in adult mammals (Benedict(*b*), 1916).

Sufficient knowledge of purin metabolism has now been attained by the new methods of blood and urine analysis to guide physicians in their

treatment of gout. Although uric acid itself is probably not the toxic substance in gout, yet there is an undoubted disturbance of nucleic acid metabolism of which hidden trouble uric acid is the outward sign. In gout there is a constant increase of uric acid in the blood, an increase in the tissue fluids much above the normal which can easily be demonstrated by the administration of phenylcinchoninic acid (atophan, cinchophen), and a deposition of sodium urate in certain locations. In addition there is a diminished excretion of uric acid after foods rich in purin are fed or after the intravenous injection of uric acid. However, this diminished excretion of uric acid, McClure and Pratt have shown, is not pathognomonic of gout, and their results have been supported by the recent studies of Bürger and Griesbach.

So many problems connected with gout are unsolved that the scientific conceptions held to-day regarding treatment should always be viewed critically and be subjected whenever possible to clinical tests. Otherwise we may fall into as serious errors as our predecessors. One illustration of what is meant may be permitted. Sweetbreads contain a large percentage of purins. Their administration to gouty patients has been promptly followed by an acute attack of gout in my own experience and that of other physicians. Weintraud(*a*) in 1895 showed that their administration to a healthy person increased greatly the output of uric acid, and this observation has been repeatedly confirmed. Yet in 1907 Arthur Luff, an English writer, in a book of much value made the following statement which has been frequently quoted by other writers with apparent approval excepting Garrod and Llewellyn: "From Walker Hall's experiments it would appear reasonable to administer sweetbread to gouty patients, since its nuclein portion is only slightly absorbed, for thymus sweetbread contains principally adenin, which is rapidly excreted, and pancreas sweetbread contains mainly guanin, and aminopurin which is incapable of increasing the urinary purin output and of exerting any injurious effects upon the tissues."

As has been said, if Luff had fed sweetbreads he would have found that in spite of Walker Hall's conclusions, the amount of uric acid in the urine was greatly increased. It is now known that animal as well as plant nucleic acid contains one guanin mononucleotid and one adenin mononucleotid, in other words adenin and guanin in equal amount, and that these both in all probability leave the intestine and enter the circulation while in the combined form either as nucleotids or nucleosids.

Diet in Acute Gout.—In the treatment of this condition there is general agreement. The diet should be light. For the first day and probably for several days the less food the better, but fluids should be given freely. For the first twenty-four hours in a severe case with nephritis I gave only water and lemonade. Milk has been advocated since the days of Sydenham. Diluents and farinaceous food until the attack begins to

abate was Garrod's practice and one generally commended. The list of foods after the first day or two would include bread, arrowroot, sago, tapioca, milk, thin gruel, barley or toast and water. After the local inflammation has subsided a larger quantity of food may be allowed, but even then Sydenham's view that everything beyond what is absolutely required for the nourishment of the body only feeds the disease is probably correct.

Diet in Chronic Gout.—In the light of present knowledge, the proper course is to give the patient a purin poor diet. Allbutt puts it well when he says that the "guiding scientific principle of the permanent diet of the gouty is to reduce the intake of the purin substances and to estimate the metabolism by examination of the urine and blood." I believe one should strive to reduce the purin substances in the diet to the minimum and to urge the patient, if the case is at all severe, to follow the diet rigidly for months and years. It cannot be made purin-free strive as we will. Much depends on the severity of the disease. In mild cases definite amounts of purin food possibly may be allowed one or two days in the week, and in six months or a year if no symptoms return the diet may be made more liberal. It is safer in this serious disturbance of metabolism, even when its symptoms are mild, to adhere for years to the purin poor diet but care should be taken that it is not too low in protein or in calories. Few patients are willing to deny themselves the pleasures of the table for many months after symptoms have disappeared. I have had one patient who followed a strict purin poor diet for six years and remained in rugged health until symptoms of heart failure developed.

If attacks recur in spite of the purin-poor diet, and in some cases they certainly do, it is a mistake to abandon it. Perseverance in this course of treatment may show benefit only after many months (Minkowski(*l*), Kraus (*e*)). It is to be understood that the diet must be one that appeals to the patient. With care menus can be arranged to satisfy the individual desires of different patients. The nutrition should not be too greatly reduced and this will not occur if pains are taken to give appetizing food.

We can speak with greater certainty of the uniform benefit of a long continued purin-poor diet in gout from the effect of the purin-poor diet which the German people were forced to adopt during the war. This was virtually an experiment on a gigantic scale applied to all gouty patients in Germany. Before the war gout was rapidly increasing in that country. Apparently from published statistics Umber and the staff of Kraus's clinic saw more cases of gout in one year than are to be found in all the hospital clinics combined in the United States and Canada. During the war gout patients remained free from attacks (Kraus(*e*), Brugsch(*g*), Griesbach and Samson).

It should be remembered that a meatless diet is not necessarily a diet very poor in purins. Beans, peas, mushrooms, asparagus, onions and

oats contain a relatively large amount of purins and they should be prohibited.

White bread, rice, tapioca, cabbage, cauliflower and lettuce are almost purin free.

Animal foods vary greatly in their purin content. The richer an organ or tissue is in cells the greater the amount of nucleic acid and its derivatives. Thymus gland which is composed of cells with large nuclei is richer in purins than any other organ. It contains about 1 gram of purin substance to 100 grams of thymus. Kidney and liver contain about one-third gram purin per 100 grams and muscle (beef, lamb) only 1/10 as much as thymus, milk only a thousandth part. Oysters and other shell fish are relatively rich in purins. Caviar and other fish roe are said to to be purin free. I found, however, that the feeding of haddock roe to one of my gouty patients produced a marked increase in the output of uric acid. Fish contains about as much purin as meat and sardines and other small fish more than beef or pork. There is no essential difference in the amount of purin in red and white meat. The old idea that white meat and fish contain less extractives than red meat is an error that is hard to dislodge from medical practice. Boiling removes a large percentage of the purin substances, and hence boiled meat with the extractives removed is less injurious for the gouty than that broiled or roasted.

Beef tea is very rich in nucleic acid derivatives, and so are meat stocks which are used in practically all soups served in hotels, except tomato soup. A meat diet is an acid diet as its catabolism in the body leads to the formation of ions (sulphuric and phosphoric acids). Vegetables are rich in cations, and when a patient is on the prescribed purin poor diet there is the possibility of an alkali excess sufficient to exert injury. Hence it is well to give dilute hydrochloric acid (15 to 30 drops thrice daily) regularly to gouty patients who are taking diets largely composed of vegetables.

Fruits likewise tend to increase the alkalinity of the urine, a fact known to the elder Garrod (1859).

Many have held that the diet should be low in calories and emphasize the fact that reduction of the quantity of food is as important as the change in quality. Among recent writers McPhedran advises a low caloric diet, while Brugsch thinks the caloric value should be normal. There is no doubt that it should be low in obese, gouty patients.

Umber believes that the diet should be low in proteins as well as low in purins. Kraus and Brugsch on the other hand insist that it should not be poor in proteins. Brugsch advises that 10 to 15 per cent of the calories of the prescribed diet be made up of protein. This is given chiefly in the form of milk, white bread, eggs and cheese.

It should be borne in mind that the ingestion of large amounts of purin free protein produces an increase of the uric acid output as Mares, Hirschstein, Höst and others have shown. The increase of the endogenous

uric acid from this source possibly has no clinical significance. It takes a very large amount of these proteins to produce only a slight increase in the uric acid excretion.

The effect of the purin poor diet in reducing the uric acid content of the blood in gout should be studied whenever possible. In this disease blood analyses are much more important than urine analyses. In spite of the exclusion of exogenous purins the blood uric acid usually drops slowly. This shows that the high value in gout is due chiefly to increased endogenous formation. Steinitz(*c*) found in a case of gout placed on a purin poor diet that the amount of uric acid was 4.9 mg. per 100 grams of blood after four days, 5.5 mg. after three months, and 3.5 mg. after six months. In one of my patients whose blood I followed for six years there was slow diminution of the uric acid in the blood, but it did not reach normal until he had been on the purin poor diet for nearly two years.

In those cases in which no benefit is said to result from a purin poor diet it would be instructive to follow closely the uric acid content of the blood. It is possible that some of these patients were continuing to eat purin foods without their physician's knowledge. It may be that the diet was not continued sufficiently long to diminish notably the uric acid content of the blood and tissues.

It is possible that attacks may continue in spite of the reduction of uric acid in the blood to the normal. I had two cases in which the blood uric acid was not increased, but there may have been an excess of uric acid in the tissue fluids. The atophan test should be tried in such cases to determine whether or not the uric acid in the tissues is increased.

Fruits of all kinds are of value in gout and should be given freely. They are free from purins. There is a prevalent idea in England that strawberries are injurious, and Sir Archibald Garrod prohibits their use. I see no reason for this and clinical evidence if it exists has never been presented. Linnæus thought strawberries had a curative power in gout.

Alcohol disturbs uric acid metabolism as Pollak showed and its use should be prohibited. Wines and beer seem more injurious than distilled spirits. In beer the purin content derived from the yeast is considerable. In a liter of Munich beer there is as much purin as in 100 grams of beef.

All writers agree that water should be taken in large amount. The reputed efficacy of mineral waters is probably due to this valuable therapeutic agent they have in common rather than to their other chemical constituents. The cause of the beneficial action of water is unknown. The uric acid output is not increased by diuresis as is sometimes maintained.

Sodium chlorid diminishes the solubility of urates in blood plasma. This was first shown by Sir William Roberts who held that the use of table salt should be restricted. He advised potassium chlorid as a substitute.

Calcium has a marked action in checking the output of uric acid as shown by the recent work of Lubieniecki, Abl, Bain and Starkenstein.

This is due apparently to a diminished formation of uric acid. Bain holds that the calcium content of foods may have an injurious effect in gout.

Care should be taken to avoid the accumulation of an excessive amount of alkali in the body. Fruits as well as vegetables increase the alkaline store. Alkaline mineral waters should be taken in limited amounts if at all. Sir William Roberts observed fresh attacks of gout apparently brought on by drinking alkaline waters, such as those at Carlsbad.

The experiments of van Logheim offer a reasonable explanation for the injurious action of alkalies and the favorable effect of acids. He produced tophi by injecting uric acid suspended in water under the skin of rabbits. The introduction of HCl per os hindered the deposit of urates and the inflammatory reaction, while large doses of alkalies hastened the formation of tophi. His results received confirmation from Silbergleit. Pfeiffer(*b*) injected uric acid subcutaneously in men and found that the inflammatory action was lessened when large doses of mineral acid were taken, while the administration of alkalies increased the local inflammation. Falkenstein introduced a hydrochloric acid treatment in gout consisting of very large doses of acid. The theory on which he based this has been discredited, but it is well to give 1 to 2 c.c. of dilute HCl three times daily when the patient is on an alkaline diet.

Caffein and theobromin are methyl purins. It is doubtful if they are converted into uric acid in the body. The methyl purins of normal urine could be formed by the removal of the methyl group, occupying position 3, from caffein and other methylated purins of food. Krüger and Schmid held that the methyl groups are decreasingly stable in the order, 7, 1, 3.

Benedict reported a carefully conducted experiment which indicates that caffein does slightly increase the excretion of uric acid. Mendel and Wardell found that the addition of strong coffee infusion to a purin free diet causes a marked increase in the uric acid output. Kaffee-Hag, a decaffeinated coffee product, had no effect.

The increase is possibly due to demethylation and oxidation of a small percentage of the ingested caffein. Brugsch thinks the caffein simply mobilizes the uric acid in the body. He holds that normally uric acid is deposited in the liver, and that caffein facilitates its entrance into the blood stream.

In dogs caffein increased both the uric acid and the allantoin excretion (Schittenhelm). While the evidence at hand does not clearly show that coffee, cocoa and tea are injurious in gout, it is the safer course to interdict their use, at least in the severer cases.

Atophan Therapy.—Nicolaier and Dohrn in 1908 found that phenyl-cinchoninic acid (2-phenyl-quinolin—4 carboxylic acid) increased greatly the output of uric acid. It was introduced into therapeutics under the name of atophan. It is also known in America as cinchophen, which is another trade name for the same substance. The word atophan, like the

term adrenalin, is so fixed in the literature that it will be difficult to supplant it. 2-phenyl-quinolin—4 carboxylic acid was described by Doebner and Giesecke in 1887. It is insoluble in water and has a bitter taste. Other members of the oxyquinolin carboxylic group increase uric acid excretion. One of these used in medicine has not the unpleasant taste of atophan. It is ethyl 6-methyl—2-phenyl-quinolin—4 carboxylate. This is called novatophan. It is sold also under the name of tolysin. This substitute can be employed in cases in which atophan is poorly borne by the stomach. This has been my experience and that of many physicians. Haskins(*b*), however, in observations on normal persons found that the increased output of uric acid was less after novatophan than after atophan.

Atophan was first used in gout by Weintraud(*b*). In this disease as in normal subjects it causes a marked increase of uric acid excretion. The rise is frequently 100 to 200 per cent in twenty-four hours. When uric acid is introduced intravenously in gouty subjects usually only a small percentage is excreted, and in some severe cases none at all. When atophan is given at the same time the increased output of uric acid may be equal to the entire amount of uric acid injected, and sometimes the extra excretion is much more than 100 per cent.

Sodium nucleate when given to gouty patients is usually in great part retained. Under the influence of atophan it is excreted quantitatively by these patients (Frank and Bauch). It is also true of all foods containing purin in large amount, that when atophan is given at the same time the uric acid output is increased in amount nearly equal to that of the exogenous purin fed.

Deutsch determined the effect of atophan (1 gram three times *pro die*) on the healthy kidneys, after feeding 300 gm. of thymus. For the first 8 hours after the purin meal the uric acid output was maintained at about the same high level, which was 36 to 38 mg. per hour above the normal.

The increased excretion may begin thirty minutes after atophan is given (Frank and Pietrulla), or the onset of the uric acid "flood" may be delayed for two or three hours. The urine in forty-five minutes from the time the drug is taken may be turbid from urates. These urates are interesting from their circular shape, radial striations and double refraction (Frank and Bauch).

When atophan is given to healthy subjects in doses of from three to five grams a day, the increased elimination of uric acid rarely continues beyond the first day. On the second day the output is usually normal or subnormal (Weintraud, Dohrn). If the administration of atophan is continued the output may be high for two or three days. In exceptional cases, however, Griesbach and Samson observed a slow increase in the uric acid output reaching its maximum on the third day. Haskins noted a period of depressed output after the atophan is discontinued. This has been confirmed by Starkenstein(*c*).

In gout the increased output of uric acid persists for a long time if the administration of the drug is continued. Study of published analyses shows that the excretion of uric acid has remained above the normal until the atophan was discontinued or the uric acid determinations were ended.

In one of Weintraud's patients with chronic gout 3 grams of atophan were given daily for 12 days and the uric acid output continued to be 200 or more mg. above the daily endogenous level throughout this period. Bauch in a case of gout gave three grams of atophan daily for thirteen days. The patient excreted three grams of uric acid in excess of the average endogenous output. One of Graham's patients excreted 0.84 gram of extra uric acid during three days that atophan was given. In health Haskins found the rise above the endogenous level averaged more than 200 mg. during the first twenty-four hours under the influence of atophan. In gout it is often much more than this, amounting to 520 mg. in one of Folin and Lyman's cases. I have seen one case of gout in which atophan caused no increased output of uric acid. It was one of polyarticular arthritis and the endogenous level was high at the time atophan was given.

Uric acid occurs in the tissue fluids as well as in the blood. Injected into the blood it disappears very quickly. Ten minutes after the injection Pratt and Russell found that the uric acid content of the blood was practically the same as before the uric acid had been introduced. It is possible that there are special depots of uric acid in certain organs. Brugsch (*e*) and Rosenberg(*a*) hold that the liver stores up uric acid as it does glycogen, fat and protein. Fine(*a*), however, found but little more uric acid in the liver than in other organs. It is possible that it exists not in a free state, but in a combined form that would have escaped detection by the method of analysis employed by Fine.

Graham has clearly shown that the extra uric acid excreted in the urine after atophan cannot come solely from the blood as the total amount of uric acid in the blood is much too small. The short duration of the increased output in health, 1 to 3 days, seems clearly due to the fact that the stored uric acid is small in amount, while in gout, a disease characterized by a tendency to deposit uric acid in the tissues, extra uric acid continues to be excreted under the influence of atophan for weeks or possibly months, because much uric acid is stored in the organs and tissues even when no tophi are present. In the spring of 1918 when the food shortage was acute in Germany Griesbach and Samson gave atophan to subjects without any increased output of uric acid resulting. This observation supports the idea that some uric acid is normally deposited in the tissues, and this store is the chief source of the increased output produced by atophan in healthy persons.

One would expect the increased output of uric acid to continue under the influence of atophan until all the excess in the tissues has been removed. For this reason it would seem a good plan to continue the administration

of atophan until the uric acid output dropped to the previous endogenous level. Brugsch(*f*) states that this may occur in some cases of gout within a few days, but I have not seen any chemical reports that supported this statement. In polyarthritis urica Brugsch gave atophan daily in 1 to 2 gram doses for a year. The excretion of uric acid continued to be high during this entire period. There were no signs of renal irritation. In so-called renal gout, that is, gout with marked renal insufficiency, the same writer found that atophan exerted little effect on the uric acid output. Fine and Chace(*c*) presented evidence that in ordinary nephritis not associated with gout the atophan exerted little or no effect on uric acid elimination.

When a patient with gout is allowed a purin meal on one or two days of the week it is well to give two or three grams of atophan on those days.

Skorczewski observed an increase of neutral sulphur after the administration of atophan, and he further claimed that urochrome was increased. It was later shown that this is not true. The positive diazo reaction obtained after giving atophan has no significance as it is due simply to derivatives of the drug itself (Greinert).

Atophan, as Folin and Lyman first showed, reduces the amount of uric acid in the blood. Their observations were confirmed by McLester, Bass, E. Frank(*d*), Steinitz(*a*), and Fine and Chace(*a*). McLester gave a patient whose blood contained 2.4 mg. of uric acid 3 grams of atophan at 9 A. M. Three hours later the amount of uric acid was cut in half and at 3 P. M. only 0.7 mg. was present. Steinitz observed a fall in the blood uric acid content from 4.8 mg. to 3.7 mg. after a dose of atophan. Retzlaff and also Gudzent, Masse and Zonder claim that in all the cases they studied atophan increased the blood uric acid. Their results are probably due to the use of faulty methods of chemical analysis. Griesbach and Samson in a recent paper state that at the end of twenty-four hours they found the uric acid in the blood nearly always diminished and never increased. They did find, however, in some cases an initial rise of the blood uric acid above the endogenous level. This increase in persons not on a purin poor diet may extend over several hours. In one of their cases the uric acid rose from 3.7 mg. to 5.7 mg. in half an hour after the administration of three grams of atophan. Their findings are important if true, but need confirmation before they can be accepted.

It is quite possible that atophan removes uric acid from the plasma and not from the blood corpuscles (Frank and Pietrulla).

After the discontinuation of atophan the uric acid increases rapidly in the blood. In the experiments of Fine and Chace it returned to the original level twenty-four hours after the last dose of atophan.

Weintraud held that the atophan exerts a selective action on the kidneys, "an elective increase of a partial function of the tubuli contorti," which causes a freer excretion of uric acid. The renal theory of atophan

action has been accepted by Folin and Lyman and by American investigators generally. The drop in the blood uric acid offers strong support for this view.

The increased output of uric acid is certainly not due to increased purin metabolism for the following reasons: (1) The allantoin excretion in mammals is not augmented by atophan (Starkenstein, Pohl(*e*)); (2) the uric acid in the blood would be higher not lower if more uric acid were formed in man; (3) the phosphorus metabolism is not increased.

Atophan not only stimulates the kidneys to secrete more uric acid, but it seems also to "mobilize" uric acid, that is, it facilitates the transport of uric acid from the tissue juices to the blood. It is, however, possible that the removal of uric acid which is the end product of purin metabolism in man from the blood by the kidney is the cause of an increased passage of uric acid from the organs and tissues to the blood. Rosenberg in perfusion experiments with the dog's liver found that the addition of atophan to the blood passed through the liver caused an increased discharge of uric acid from that organ, and this work certainly supports Brugsch's mobilization theory. Griesbach's recent observations suggest that atophan tends to check the storage of uric acid in the tissues. In addition Starkenstein's careful studies indicate that the drug has an inhibiting action on the whole purin metabolism. This shows itself in the normal man in the diminished output of uric acid that occurs after the administration of atophan is stopped and during its use when continued for more than a few days.

Atophan has then a fourfold action. It increases the excretion, sets free stored uric acid, prevents further storage, and inhibits purin metabolism. "The action of the drug presents many analogies with that of phloridzin, and one may look on the process in the light of a temporary renal uric acid diabetes" (Hopkins and Wolf).

Tophi have been seen to diminish under the long-continued action of atophan. Weintraud referred to such a case in his first paper, and Llewellyn, a physician with large experience at Bath, England, says, that he has been much impressed with the manner in which it produces softening and diminution in the size of tophaceous deposits.

Atophan has been found useful in acute attacks as well as in chronic gout. It quickly lessens the pain. Brugsch would not give the drug during the attack, but in acute cases only immediately before or immediately after the attack. His reason for so doing is that the uric acid output is high during the height of the attack and that atophan at that time will only raise the output but slightly. Before and after the attack the excretion is usually low, and then atophan causes a great increase in the excretion. The usual amount is 3 grams daily, in divided doses of 0.5 gram each. It is a good plan to give the patient a supply of atophan with instructions to take it as soon as premonitory symptoms appear. In this way possibly a severe attack may be prevented.

Atophan in my experience frequently produces symptoms of hyperacidity. To prevent digestive disturbances the employment of the small dose of 0.5 gram frequently repeated should be tried, rather than the common habit of giving large doses once or twice a day. The drug should be taken with plenty of water. Sodium bicarbonate should be given with each dose of atophan if there is a history of gravel, as renal colic has occurred after the administration of atophan in cases of nephrolithiasis. Give 10 to 15 gm. of sodium bicarbonate on first day and 5 to 10 gm. on subsequent days. On the other hand as alkalies seem injurious in gout sodium bicarbonate should not be added to atophan as a routine procedure.

Some patients have a strong idiosyncrasy against atophan. Diarrhea, vomiting, severe headache, and tinnitus have been produced by the drug according to Brugsch and on their development its use should be abandoned, and the milder preparation, novatophan (tolysin), employed.

Colchicum.—This drug may be fairly accounted a specific in the acute paroxysm of gout and has enjoyed a deservedly high reputation for generations. It has "the property of easing, in an almost magical manner," the pain of gout. The wine of colchicum is a favorite preparation. The dose is 1 to 2 c.c. three times a day for two or three days. It may be of advantage to give a large dose at first, 2 to 4 c.c. and follow this up by much smaller doses as the elder Garrod suggested. Allbutt(*b*) gives it in a mixture of laxative drugs half an hour before meals. In my hands it has been less effective than the alkaloid colchicin which can be obtained in granules, each containing 1 mg. Three or four may be given the first day of an acute attack in doses two to four hours apart. Relief from the pain is usually experienced after a few hours. On the second day the drug is given in the same dosage, but instructions should be left with the patient to stop the medicine if diarrhea or vomiting occurs. It is well to follow the colchicum with a course of atophan.

How colchicum produces its favorable action is unknown; possibly through increasing the circulation through the inflamed joints as recent experimental work would indicate. It does not cause an increased output of uric acid as Chace and others have shown.

Other Methods.—If the pain is very severe morphin should be used so that relief may be obtained in the interval of hours that always elapses before the benefit from colchicum is apparent. English writers urge the importance of a brisk purge. For this purpose Allbutt(*b*) prefers a blue pill to which 0.1 to 0.2 of a gram of extract of colchicum is added. He would give this for the first two or three nights of an attack. Personally I have not used purgation. As colchicum pushed to the physiological limit produces diarrhea I do not wish to lose this valuable warning that the limit of safe administration has been reached. A mild laxative may be given at the onset of the attack. If a saline is given magnesium sulphate is preferable to salts containing sodium (Roberts).

It has long been known that the salicylates cause a significant increase in the output of uric acid (Rockwood, Pietrulla). Fine and Chace(*b*) held that sodium salicylate acted better than atophan in the removal of uric acid. Twice it caused an almost complete disappearance of uric acid from the blood. In one case of gout eight grams of sodium salicylate reduced the blood content from 4.4 mg. to 3.2 mg. The eight grams of sodium salicylate were given for two more days, and the uric acid fell further to 1.4 mg. Denis(*a*) gave eight grams of sodium salicylate daily for three days in a case of gout. The uric acid in the blood fell from 4.1 mg. to 0.4 mg. Aspirin has a similar action.

Large doses of salicylates are required to produce this effect and a small dose, that is, one under two grams daily, may even cause a lessened output (Fauvel). Atophan on the other hand in a dose of 0.5 gram may increase the uric acid excretion more than 100 per cent and even 0.25 gram has raised the output 13 to 18 per cent (Nicolaier and Dohrn). Denis found that an amount of sodium salicylate as high as 3.3 grams (50 grains) in a day had no effect on the uric acid output.

Some physicians have claimed good results from the use of salicylates in gout, but on the whole it has not been highly esteemed in this disease. If there is intolerance to phenylcinchoninic acid and its derivatives the salicylates should be employed. One should remember that large doses are necessary, 5 to 8 grams daily, in order to increase the uric acid output.

In acute attacks rest to the inflamed parts is absolutely necessary. Warm dry applications lessen the pain more than moist compresses. As soon as the acute paroxysm has passed the patient should be enjoined to leave his bed and exercise in increasing measure. During convalescence, massage and gymnastics may be of value. The diseased joints should be protected from injury or excessive exercise. If this is not done the inflammation may quickly return.

Exercise in the intervals between acute attacks and in chronic gout is undoubtedly of great importance. The manner in which it acts so beneficially is unknown. Sometimes exercise seems to increase the uric acid output, but many observations have been made in which there was no increase after exercise (Sherman).

Gentle exercise in the open air should be taken regularly. An incentive should be found to lure the patient out-of-doors. Horseback riding, rowing and golf are forms of exercise well suited to gouty persons.

Local electric light baths are often useful in chronic gout. In robust patients with strong hearts much benefit may result from sea baths.

Radium emanations have been highly extolled, especially by His and his pupils. Fine and Chace in careful experiments found that neither the intravenous administration of the bromid nor inhalations for long periods in strengths as high as 100 Mache units per liter influenced the uric acid content of the blood.

TABLE OF FOODS WITH THEIR PERCENTAGE OF PURIN-NITROGEN AND URIC ACID PRECURSORS FROM ESTIMATIONS BY WALKER HALL

		Percentage of Purin-Nitrogen	Calculated as Uric Acid per 100 Grams
Fish:	Cod	0.0233	0.0699
	Plaice	0.0318	0.0954
	Halibut	0.0408	0.1224
	Salmon	0.0466	
Meats:	Tripe	0.0229	0.0687
	Mutton—Australian	0.0386	0.1158
	Veal—Loin	0.0465	0.1395
	Pork—Loin	0.0485	0.1458
	Neck	0.0227	0.0681
	Ham	0.0462	0.1386
	Beef—Ribs	0.0455	
	Sirloin	0.0522	0.1566
	Steak	0.0826	0.1365
	Liver	0.1101	0.3303
	Thymus	0.4025	1.2075
	Chicken	0.0518	0.1554
	Turkey	0.0504	0.1512
	Rabbit	0.0380	0.1140
Cereals:	Bread—White	No trace	
	Oatmeal	0.0212	0.0636
	Rice	No trace	
Pulses:	Peameal	0.0156	0.0468
	Beans (Haricot)	0.0250	0.0765
	Lentils	0.0250	0.0750
	(malted)	0.0150	0.0450
Roots and tubers:	Potatoes	0.0008	0.0024
	Onions	0.0031	0.0093
	Tapioca	No trace	
Green vegetables:	Cabbage	No trace	
	Lettuce	No trace	
	Cauliflower	No trace	
	Asparagus (cooked)	0.0086	0.0258
Beers:	Lager beer	0.0050	0.0159
	Lager drink	0.0020	
	Pale ale	0.0059	0.0177
	Porter	0.0060	0.0186
Wines:	Claret, Volnay, Sherry, Port	No trace	
Tea:	Ceylon	0.0164	0.0805
	Indian	0.0147	0.0700
	China	0.0107	0.025-0.046
Coffee:		0.0294	0.110-0.250

Treatment at spas has been held in high favor. Benefit comes from the healthful life rather than from any special property of the waters.

The American springs best suited to gouty patients are Hot Springs, Ark., Hot Springs, Va., White Sulphur Springs, W. Va., Bedford, Va., (Foster). "Two or three months' camping, with much rowing, sailing, canoeing and fishing often proves highly beneficial to gouty patients, provided that appetite is kept within control. Many a gouty individual has gotten a new lease of life by spending a summer judiciously in the Adirondacks or Rocky Mountains, on the coast of Maine, in the Wisconsin or Michigan woods or among the 30,000 islands of the Georgian Bay" (Barker(*b*)).

Renal Calculi Including Phosphaturia and Oxaluria

. . . . . *Jacob Rosenbloom*

Introduction—Metabolic Studies—Phosphaturia and Phosphate Stones—Phosphorus Metabolism—Calcium Metabolism—Magnesium Metabolism—Oxaluria and Oxalate Calculi—Uraturia and Uric Acid Calculi—Xanthin Calculi—Cystin Calculi—Dietetic and Medicinal Treatment of the Various Varieties of Urinary Calculi—Phosphate Calculi—Uric Acid Calculi—Oxalic Acid Calculi—Diet Scheme in Oxaluria—Xanthin Calculi—Cystin Calculi.

Renal Calculi Including Phosphaturia and Oxaluria

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I. Introduction

Before a pathological concretion may form it is essential that there be a nucleus of some substance different from the substance to be deposited. Upon the nucleus substances crystallize out of solution and only in a few cases would the concretion form, were it not that the solution contains an excess of some substance. However, the nucleus may, in certain instances, cause the precipitation of the substance. Concretions consist, therefore, of mixtures of colloids, and crystalloids deposited from the solutions of colloids and crystalloids, and, on this account, the application of the principles of colloidal chemistry throws considerable light on the conditions of their formation. It is to be remembered that the constituents of urinary calculi are derived from the secretion of the kidneys and are usually deposited on account of an oversaturation of the urine or on account of a change in the composition of the urine, which renders them insoluble. Although the amount of colloidal material in the urine is small, it plays an important part in keeping in solution the less soluble crystalloids, such as urates and calcium oxalate. In inflammatory conditions fibrinogen appears, which readily forms the irreversible fibrin, and conditions thus become favorable for the formation of concretions made up of any crystalloid that the urine may be saturated or oversaturated with at that time. Aschoff and Kleinschmidt claim that most urinary calculi begin as primary calculi formed independent of any inflammation, but from an excess of the main constituent (uric acid, oxalates, xanthin, ammonium urate); this calculus then forms the crystalline nucleus of the laminated secondary deposit of other substances (uric acid, oxalates, and phosphates); all being deposited without inflammation. The inflammatory formations are usually deposited on a foreign body or a primary calculus and are composed chiefly of ammonium-magnesium phosphate and ammonium urate.

Urinary calculi commonly consist of the following substances: uric acid, ammonium urate, xanthin, cystin, calcium carbonate, calcium oxalate, calcium and magnesium phosphate (the so-called bone earth) and

triple phosphate (ammonium-magnesium phosphate). The indigo, urostealith, fibrin, cholesterol, silicic acid, hematoidin, magnesium urate, protein, blood and bacteria calculi are very rare and there is practically nothing to be noted as regards their metabolic interest or treatment at this time. It was formerly taught that most urinary stones are composed of uric acid, or urates, but recent studies show that this idea is wrong, and that the majority of urinary stones are composed of calcium salts. These studies also show that it is impossible to determine the nature of the stone by microscopic examination, that the only method is to examine it chemically, and the treatment instituted should be based on the character of the stone. It is especially important that those subject to urinary lithiasis should be treated along the lines suggested, after the nature of the stone or gravel has been determined, as it is only by this procedure that we may be able to prevent the formation of new stones or the further growth of the primary stone.

II. Metabolic Studies

Phosphaturia and Phosphate Stones

The cardinal symptoms of phosphaturia are the presence of a cloudy or milky urine, of usually an alkaline reaction, occasionally neutral or amphoteric and rarely weakly acid. This cloudy urine has interested physicians from early days in the history of medicine. To understand its origin we must consider certain facts regarding the metabolism of the substances that form this precipitate.

Phosphorus Metabolism

The phosphorus in our food and in the organism is never in its molecular form, but always as its salts and as esters of orthophosphoric acid. The salts are the primary and secondary phosphates of sodium, calcium, potassium and magnesium, all of which can be resorbed in the digestive tract. The extent of resorption of the soluble and insoluble phosphates is dependent on the acid or alkaline reaction and the concentration of the calcium and magnesium ions present, and is, consequently, very variable. Phosphoric acid is found incorporated in the molecule of protein bodies, the phosphoproteins of which the chief representatives are casein of milk and the vitellin of the egg yolk and as a constitutent of nucleoprotein.

The sulphuric acid (sulphate ion) arising in metabolism from the oxidation of the protein sulphur requires two cations with which it circulates in the blood and is excreted in the urine. As the sulphate ion corresponds to a strong acid, since a sulphuric acid in the strength here considered is completely dissociated, it cannot take two hydrogen ions with it into the urine since an acid reaction of such a strength is not possible.

The sulphate ion takes, therefore, two alkali ions at its excretion from the body. The weaker an acid is, the smaller is its dissociation, the more hydrogen ions it can bind, and the more alkali it can take from the organism. The excretion of hydrogen ions is necessary for the carnivora and omnivora in order to maintain the neutral reaction, and this excretion is effected above all by phosphoric acid. From the disodium phosphate of the blood is produced through the action of the kidney the monosodiumphosphate of the urine, which dissociates in the urine and is the essential cause of its acid reaction.

The carbonic acid, when given up to the lung, fulfills the task of a quantitative sparing of alkali to the organism. But into alkaline urine varying quantities of H_2CO_3 enter and fix alkalis. That is advantageous for the herbivora since they consume in abundance the alkaline salts of oxidizable acids, which constantly furnish the organism with cations. But when a meat-eating animal produces an alkaline urine continuously without being furnished with sodium bicarbonate or alkalis of organic acids, the entire organism must undergo a change leading first to an alkali loss and second to a compulsion to remove by some other way the hydrogen ions which it does not give off to the urine.

Calcium Metabolism

Calcium is brought to the organism in inorganic form in the food; in the milk in a complex protein phosphoric acid compound. The amount of resorption is dependent on the reaction in the gastrointestinal canal since in acids, calcium carbonate and phosphate are soluble. If the food is rich in phosphates relatively less calcium is resorbed. Only a part of the resorbed Ca appears in the urine. The amount of resorption is difficult to determine because the intestine is also an important excretory path for calcium. What portion of the fecal calcium has passed through the body cannot be determined. That an alkaline reaction and a higher content of soaps in the large intestine lead to an increased elimination of calcium through the intestine has been shown especially by the pediatrists.

The daily calcium need of the human adult is less than 1.29 gm. (Renwall(*a*)). According to the investigations of Bertram, calcium equilibrium can be maintained with less than 0.49 CaO gm. (= 0.2869 gm. Ca). Of especial importance is the partition of excretion between kidney and intestine. According to Renwall 25.4 to 64.3 per cent of the total Ca goes through the kidney in adults; 32 per cent in sucklings (Blauberg). The cause of these great variations in the adult is still not clear; probably the kind and quantity of food have an influence.

Healthy adults appear to possess a tendency to calcium equilibrium, yet with a pure milk diet calcium retention takes place. The amount of urine calcium is 0.33 gm. to 0.80 gm. CaO per day.

Magnesium Metabolism

Magnesium is supplied almost exclusively in inorganic forms; its resorption is less dependent than that of calcium upon the reaction in the intestine. According to Renwall 29 to 34 per cent of the total magnesium appears in the urine (with free choice of food 36.2 to 37 per cent). According to Bunge(*b*) the magnesium need of the adult is at most 0.69 gm. per day. In 24 hours 0.14 to 0.29 gm. MgO are excreted in the urine.

The precipitation of phosphates and carbonates with calcium and magnesium takes place in neutral and alkaline urines, only seldom in acid urine.

An alkaline reaction in human urine may be the result of a vegetable diet or the use of alkaline salts; that is of an exogenous origin. But an alkaline reaction may occur from internal causes, as when great amounts of acid are excreted in the stomach, that is, in normal circumstances, in the hours of abundant gastric digestion. If the hydrochloric acid of the gastric juice is lost by long continued vomiting, the stomach, whose glands possess to a high degree the ability to concentrate hydrogen ions, becomes an excretory path for hydrogen ions, and the kidneys, in order that the neutral reaction may be conserved, must give out hydrogen ions. Alkaline urine and chronic HCl vomiting stand in a causal relation so that with constant vomiting a strongly acid urine is possible only with anacidity.

If phosphate precipitation takes place in an alkaline urine produced in this way, it is not to be considered as phosphaturia. Nor do we designate as phosphaturia the cloudy urine which results from ammoniacal fermentations due to infection of the urinary tract.

As actual endogenous phosphaturia may be reckoned only cases which void cloudy, milky urine constantly or in painful attacks with nervous symptoms, and upon a diet which would normally produce acid urine. Samples of urine with evidences of phosphaturia are frequent whereas constant true phosphaturia is much more rarely observed.

Endogenous phosphaturia is mostly combined with nervous or neurasthenic symptoms or with disturbances of the stomach or urogenital system.

G. Klemperer(*c*) attempts an etiological division of phosphaturia into the following forms:

1. Phosphaturia caused by gastric hyperchlorhydria.
2. Phosphaturia caused by increased calcium excretion in the urine, a heightened "calcium avidity of the kidney."
3. Sexual phosphaturia.

The changes in the urine during phosphaturia are certainly not the result of an increased phosphoric acid excretion. On that point there is complete unanimity. According to Minkowski the separation of a phosphate sediment is always to be regarded as an expression of diminished acidity. Leo also considers the alkaline reaction as the dominant feature

and therefore names the whole process *alkalinuria*. The conception of Leo that the production of alkaline urine is a result of increased blood alkalescence is wrong, since an increased blood alkalescence does not exist. It is certain that the formation of a phosphate sediment takes place in neutral and weakly acid urine, whereas freshly voided alkaline urine may be quite clear. It has already been mentioned, that making a normally acid urine alkaline does not produce so abundant a sediment as occurs in phosphaturia. Naming the condition "alkalinuria" does not describe the kernel of the matter. Sendtner found an increase in calcium excretion of the urine in phosphaturia. Soetbeer, Krieger, and Tobler investigated the calcium metabolism of children with phosphaturia and came to the following conclusions:

Soetbeer found in the urine of a sick child 0.382 gm. CaO, in the urine of a normal child on the same diet 0.113 gm. CaO. The phosphates were the same in both. The ratio $CaO:P_2O_5$ was 1:4 in the sick, 1:12 in the normal child. The phosphaturia patient had a corresponding decrease of calcium in the feces. As the sick child had symptoms of colitis, Soetbeer regarded the increase of calcium in the urine as the result of a disturbance of calcium excretion in the large intestine. This conclusion has received no concurrence. Concerning the calcium excretion in a diseased large intestine we know nothing. Tobler's patients, who also had increased calcium output in the urine, had essentially normal stools. Tobler confirmed Soetbeer's observation. He found in a four day period:

Normal urine, 0.414 gm. CaO.

Phosphaturia I., 1.943 gm. CaO.

Phosphaturia II., 0.763 gm. CaO (three-day period).

The quantity of phosphoric acid was the same in all, the feces of the normal subject containing more calcium than the feces of the other patient.

Umber investigated adults suffering from phosphaturia. He found the ratio of P_2O_5: CaO was as 29:1 in the subject with phosphaturia as 42:1 in the normal subject. In phosphaturia there was increased calcium excretion in relation to phosphoric acid excretion. In the second period the increased calcium feeding did not increase calcium excretion in the phosphaturia patient as it did in the control subject.

The patient first retains the calcium. According to Umber the phosphate sediment is caused by too high a content of alkaline earths in proportion to the phosphoric acid content and too low an acidity. In Umber's patient 45.5 or 48.8 per cent of the total calcium was excreted in the urine; in the normal subject, 26.8 or 18.65 per cent. Umber remarks that further investigations must decide whether this partition follows any law. However, a still higher percentage of total calcium is found in the clear urine of healthy persons; the highest value obtained by Renwall was 64 per cent.

The ratio of P_2O_5 to CaO in the urine of subjects with phosphaturia

has been studied by G. Klemperer. In one of his cases the calcium of the urine on a rich calcium diet was very high. The P_2O_5 : CaO ratio varied from 4.1 to 37.1. In one of his cases a man suffering from a constant phosphaturia, excreted in the urine:

Gm. CaO	Gm. P_2O_5	P_2O_5 :CaO
0.5335	2.55	4.8:1
0.5049	3.06	6.0:1

After general treatment the urine became clear and the ratios were as follows:

Gm. CaO	Gm. P_2O_5	P_2O_5 :CaO
0.4780	3.19	6.8: 1
0.6765	3.96	5.8: 1
0.5090	3.45	6.0: 1

It may be noted that the ratios are about the same even after the condition had cleared up.

If we turn to the question of the nature of phosphaturia we must with Minkowski place its origin outside the kidney. Minkowski says: "The composition of the urine is undoubtedly determined by the special processes in the secreting elements of the kidney and it is not excluded that the selection activity of the kidney filter may be so influenced by pathological changes in itself that a decrease of the acid or an increase of the alkali output should occur." And further, "The activity of the kidney cells is undoubtedly under the influence of the nervous system and it is consequently not impossible that nervous influences should affect the acidity of the urine and by its decrease lead to phosphaturia." According to Minkowski phosphaturia is a secretion neurosis of the kidney.

When upon a normal diet a human being excretes a constantly alkaline urine the kidney fails to perform the important function of acid excretion and of alkali retention and of a loss of alkali from the body occurs. In this relation the urine in phosphaturia behaves like the urine in acidosis and there is a lessened excretion of alkalies through the intestines. On this basis we may say that phosphaturia depends upon a disturbance of the acid elimination and of the conservation of the alkaline state.

Oxaluria and Oxalate Calculi

By oxaluria we mean the presence of calcium oxalate crystals in the freshly voided urine. The formation of these crystals takes place in acid, neutral and alkaline urine. The formation of these crystals is to a great deal independent of the oxalate content of the urine.

Normal human urine contains oxalic acid in very small amounts. On ordinary diet Fürbiger found 20, Dunlop 17, Autenrieth and Barth 15 milligrams per day. This oxalic acid comes in part from the ingested food.

The resorption of oxalate in the digestive canal depends on the solubility. The greater part of the oxalic acid of vegetables is in the form of the insoluble calcium salt whose solubility is increased by the presence of hydrochloric acid. The acidity of the gastric juice is doubtless of great influence. According to an investigation by Dunlop, Mohr and Salomon, the excretion of oxalic acid in urine can be increased by feeding HCl and diminished by feeding alkalies. The amount of oxalic acid in urine, therefore, becomes with a vegetable diet very variable. But it is to be observed that even when feeding a soluble oxalate, only a small portion is excreted in the urine. G. Klemperer found that of 100 mg. oxalic acid 15 mg. were excreted in the urine, 10 mg. in the feces, while the remainder was not to be found and presumably was broken up in the intestine by bacteria. The resorption of the soluble oxalate also depends on the amount of calcium present at the same time. Consequently it does not seem strange that the most contradictory findings are made concerning the resorption and excretion of the oxalic acid from the food. Abeles found that after eating spinach containing 140 mg. of oxalic acid none appeared in the urine. Lommel(*a*) also found that after a diet rich in oxalic acid no more appeared in the urine than with an oxalic acid free diet. Whether oxalic acid is excreted by the intestines is not known. Pohl and Faust have shown that injected oxalic acid appears in the urine and we may conclude from these findings that resorbed oxalic acid is not broken down.

To the oxalic acid of the food is added as a further exogenous source, that which comes from the breaking up of other constituents of the food. This portion arises in the same way as the oxalic acid which the organism forms in its own metabolism and should therefore be reckoned with the endogenous oxalic acid.

Auerbach first established that dogs fed with meat and fat, *i.e.,* oxalic acid free food, excreted oxalic acid. W. Mills confirmed this result. Afterwards Luthje(*a*) observed that a fasting dog at the 12th to 16th day still gave out an average of 9 mg. oxalic acid in the urine and that on a diet consisting exclusively of milk and sugar. Human urine contained oxalic acid on the 11th day of this food. Mohr and Salomon found the same thing. Oxalic acid is therefore proved to be a normal metabolism product and the question arises from what does it come.

The observation that in plants and in microörganisms oxalic acid is a product of sugar led to the assumption that the carbohydrates are the mother substance of oxalic acid in man and in other animals. It is now, however, agreed that such a relationship does not exist. Fats also are no

oxalic acid producers. For a long time the nucleoproteins have been looked on as the material for the formation of oxalic acid. Upon treatment with oxidizing reagents (permanganate, iron chlorid) uric acid is easily transformed into oxalic acid. Frerichs and Wohler observed an increase in oxalic acid excretion after feeding with ammonium urate; but later with exact methods this finding could not be confirmed. Lommel once observed an increased output of oxalic acid after feeding with great quantities of calf thymus. But Luthje, Mohr and Salomon could not verify this result. Besides Cipollina found 11.5 to 25.4 mg. oxalic acid per kilo in the calf thymus; and as Lommel had given his subjects 1500 gm. of pulp, this preformed oxalic acid was sufficient to account for a rise of 30 mg., the maximum which Lommel observed. There are no observations which force us to regard oxalic acid as a product of nucleoprotein metabolism.

Oxalic acid excretion has, as Lommel showed, no relation to protein metabolism. But it undergoes, however, an increase after feeding with gelatin and gelatinous tissues (Lommel, Mohr and Salomon). Klemperer and Tritschler have concluded that it is the glycocoll of gelatin—NH_2CH_2COOH—that forms the oxalic acid. According to the investigations of E. Fischer and of Levene and Beatty gelatin contains 16.5 to 19.25 per cent of glycocoll. Glycocoll occurs also in other protein foods—100 gm. fowl protein contains 3.15 gm.; 100 gm. syntonin from oxflesh 0.5 gm.—but these amounts are so small that they furnish no conclusion in metabolism experiments. Satta and Gastaldi, contrary to Klemperer and Tritschler, found that glycocoll feeding produced no increased oxalic acid output in dogs.

Similar negative results have been found in man. W. Thörner fed five persons six times with glycocoll in amounts from 2 to 5 gm. and in no case observed increased oxalic acid output.

Long ago Kühne expressed the suspicion that creatin,

$$HN=C<\begin{matrix}NH_2\\N(CH_3).\end{matrix}CH_2.COOH$$

passes over into oxalic acid.

Klemperer and Tritschler found this suspicion verified. Creatin occurs in varying quantities in the muscles of vertebrates, being greatest in that of birds. According to Monari the amount is increased by work, if the conclusion of Klemperer and Tritschler is correct. The observations of G. Meissner and C. Voit that creatin given to an animal reappears entire in its urine are opposed to it. W. Thörner ate during two days seven partridges without having any increase in the oxalic acid of the urine.

The preformed oxalic acid of the food and that which is formed out of the food and in the body appears in the urine as oxalate. Many have tried to correlate the precipitation of the calcium salt with many morbid condi-

tions particularly with diseases of metabolism, with gout, obesity and diabetes mellitus. But all recent observations have shown that neither in gout nor in all of the diseases that manifest a disturbance of purin metabolism is there an excess of oxalic acid beyond the normal in the urine. The numerous observations of a normal oxalic acid content with increased uric acid output (leucemia, after pneumonia) also speak for a complete independence of oxalic acid formation and nucleoprotein metabolism as do the data obtained in diabetes and in obesity. The reaction of the urine has no influence on the solubility and precipitation. Sediments from strongly acid urine containing both uric acid and calcium oxalate are known to all. On the other hand, alkaline urines with a phosphate sediment are frequently free from oxalate crystals. Therefore, the solubility is not measurably increased by an acid nor diminished by an alkaline reaction.

Every urine is supersaturated in relation to its content of calcium oxalate, and the colloidal state of the urine determines the solubility of the oxalate.

Uraturia and Uric Acid Calculi

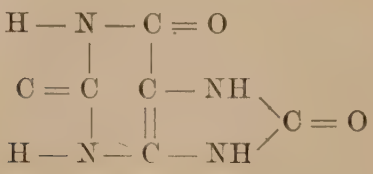
By uraturia we mean the precipitation of uric acid or its acid sodium salt or acid ammonium urate. These occur most frequently in acid, concentrated urine. The precipitation of ammonium urate is found only with a urine of high ammonium content.

It may be taken as certain that uric acid up to a vanishing fraction circulates in blood as urate ions, since the hydrogen ion concentration of the blood is not sufficient to build undissociated uric acid.

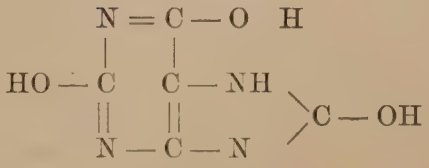
In the secretion of acid urine the urate ion joins the hydrogen ion in the kidney cell to form undissociated uric acid. In acid urine the greater part of the uric acid is present in an undissociated form, a part as urate ions. Through this transition from the urate of the blood into the undissociated uric acid of the urine, uric acid like phosphate effects an elimination of H ions and a sparing of alkali.

Acid urine represents a highly supersaturated solution. Magnus-Levy observed a urine that contained a gram of uric acid dissolved in 39.4 liters; according to Gudzent, at 37° it is dissolved in 25 liters of water. If the water be acidified to the degree of urine the solubility becomes less and uric acid precipitates. The urine behaves differently. It is but seldom that acidifying causes an abundant precipitate of uric acid. Most urines, even when concentrated, remain clear or only after hours crystallize out a small part of the uric acid.

Acid sodium urate has a far higher solubility than the uric acid. Gudzent has shown that both isomers form the urate; the unstable lactam form



and the stable lactim form



are distinguished by their solubility. The lactimurate is more stable and less soluble. According to Gudzent the watery solutions are:

	18°	37°
Acid uric acid sodium (lactam)	1:846	1:469
Acid uric acid sodium (lactim)	1:1270	1:710

Which form exists in urine we do not know. With a neutral reaction the urine water is at any rate sufficient to hold the uric acid in solution as a sodium salt. That we, notwithstanding, so often observe the sedimentium is due to the fact that the solubilities of the acid alkali urates are greatly diminished by the presence of great amounts of alkali ions ($\dot{N}a$:$\dot{K}$).

Temperature has a great influence on the solubility of acid sodium urate. It may often be observed that a precipitate which disappears after short boiling does not reappear on cooling and that the urine remains clear for hours and even days. There must therefore be a change produced in the urine by heating. Decomposition of uric acid is not in question; decrease of acidity caused by the small loss of CO_2 cannot work so great a change. One can even make the urine more strongly acid after heating without hastening the formation of a precipitate. This phenomenon of change in solubility may be found at times in urines which give a dense uric acid precipitate on acidification. If one adds the same amount of acid to the heated urine the precipitation may fail or come later. It can be shown that by boiling a change in the solubility state of the colloid is produced. Lichtwitz examined 57 such urines for their colloid conditions. The gold count was made before and after boiling and the time noted that the sediment remained in solution. The gold count increased from two to ten times, *i.e.*, the urine colloids were in a state of precipitation in these urines, and became reversible through boiling, as gelatin by warming goes into a finer separation. In 18 urines that on cooling precipitated

the gold count was the same before and after boiling, *i.e.*, the colloid which these urines contained was in an irreversible precipitation state. Such urines may be without defense action for colloidal gold solutions. Lichtwitz observed a patient who passed urine four weeks without a gold count with abundant uric acid sediment; only on one day was the urine clear and acted protectively on the gold solution.

These observations show with complete clearness the dependence of the solubility of uric acid and the uric acid salts upon the colloid state of the solution.

The concentration is of subsidiary importance for the precipitation of uric acid and its acid sodium salts. Precipitation occurs with quite normal amounts and abnormal amounts remain in solution. That other conditions being the same, a sediment occurs more readily in concentrated urine is obvious.

The reaction is of significance only in so far that only in acid urines a sediment occurs. If occasionally there is a neutral reaction in a urine, that is caused by the fact that in the crystallization process hydrogen ions have left the solution and thereby reduced its acidity. At any rate in very strong acid reactions ($(H)=1.10^{-5}$) the uric acid may remain dissolved. The dominant factor for the solubility is the state of the urine colloids.

Since the processes of sediment formation do not depend on the uric acid itself the characterization of the sediment formation as "uric acid diatheses" is quite unjustified as Brugsch and Schittenhelm have so explicitly set forth. The formation of uric acid sand and its consequences, the formation of uric acid stone, the urate stone diatheses should be clearly distinguished from the uricemic diatheses, the gout. This distinction is not always made, because gout and uric acid stone often enough occur in the same subject. This combination Sydenham observed on himself 150 years before the discovery of uric acid. The great majority of cases of urate stone diatheses occur, however, without gout. Brugsch and Schittenhelm remark that whereas in childhood gout is extremely rare, uric acid stone is most frequent. The cases in which gout and urate stone combine may be explained as follows: the gout causes deposits of acid uric acid sodium in the kidney, which come to the surface and there form a stone nucleus.

Xanthin Calculi

Xanthin or 2.6–dioxypurin, $C_5H_4O_2N_4$ was first discovered in a urinary calculus weighing eight grains by Marcet in 1817. There are several cases on record where it has been found in the urine as a sediment. Maclagan found xanthin crystals in the urine of a supposed hysterical girl; Jackson, in a case of diabetes mellitus; Bence-Jones in the urine of a boy;

Weiske in a case of leucemia in an animal; and Cottereau in the urine of a boy.

The chemical nature of xanthin was first studied by Liebeg and Wöhler, who analyzed a stone removed by the older Langenbeck. The stone was removed from an eight-year-old boy and was the size of a hen's egg. They were able to show that this stone was composed of the same substance that Marcet had described. Unger was able to verify these results. Langière recorded the third case of xanthin calculus. Lebon describes the fourth case and records a stone composed of xanthin, uric acid, phosphates, and calcium. Hoppe-Seyler mentions the fifth case, Dulk the sixth, and myself the seventh.

As xanthin is one of the mother substances of uric acid, it is quite possible that the same sort of metabolic defect is present in these cases as in the uric acid deposits.

Cystin Calculi

These calculi are very rare and of great interest. The condition of this metabolic defect will be described under cystinuria as individuals suffering from this condition are those that are apt to develop cystin calculi.

III. Dietetic and Medicinal Treatment of the Various Varieties of Urinary Calculi

(a) **Phosphate Calculi.**—The dietetic indications are to diminish the intake of calcium, thereby putting the phosphate in a more soluble form. Foods rich in calcium are therefore to be avoided, such as milk, fish, eggs, beer, wine, liquor and fruits, while meat, potatoes, cereals, broths, sugar, sweets and puddings are allowed.

Medicinally hexamethylenetetramine and acid sodium phosphate or citric acid should be given. Diuresis should be promoted by advising the use of large quantities of water. Of course in those cases where hyperacidity of the gastric juice is present, this must be treated along appropriate lines.

(b) **Uric Acid Calculi.**—It will be remembered that the uric acid of the urine has a twofold origin, the endogenous, derived from the metabolism of the tissues, and the exogenous, derived from the decomposition of the food. The endogenous is constant for the same individual and is uninfluenced by diet, while the exogenous can be profoundly influenced by diet. It must also be remembered that the precipitation of uric acid from the urine does not depend entirely upon the amount present, but very largely on the chemical relationships determining the formation in which the uric acid is excreted, and that in order for it to remain in solution in

the urine, the reaction of the urine must not be too acid and salts must be present to unite and form the necessary bases.

The dietetic indications are for a mixed diet with a preponderance of vegetables, fats, and carbohydrates, and low protein, of a purin free nature. Liver, brain, sweetbreads, kidneys and fish roe are forbidden; also game, pickled fish, shell fish, sauces, highly flavored foods, mushrooms, broths, beef-tea, meat, extracts, coffee, tea, alcoholic drinks, cocoa, chocolate and asparagus. Much salt, and all salt fish and salt meat should be avoided because uric acid is more easily precipitated from urine containing an abundance of salt.

Fats, milk, whey, milk gruels, eggs, butter, cream cheese, gelatin, peas, beans, and fruits are especially good. Enough water should be given to cause about 2000 c.c. of urine a day. The following are very good dietetic lists:

PURIN-FREE DIET

May take:

CEREALS

Cream of Wheat	Macaroni	Corn Flakes
Puffed Rice	Rice	Rice Flakes
Wheat Flour	Tapioca	Corn Starch
Wheat Bread	Hominy	Farina
Indian Corn	Cake, Plain	

VEGETABLES

Tomatoes	Egg-plant	Kale
Vegetable Oyster	Parsnips	Water Cress
Peppers	Turnips	Corn Salad
Radish	Carrots	Chard
Cauliflower	Beets	Chives
Raw Cabbage	Celery	Chicory
Lettuce	Onions	Sorrell
Spinach	Squash	Leeks
Potatoes	Endive	Rhubarb
Sweet Potatoes	Brussels Sprouts	Kohlrabi
Sweet Corn	Romaine	

FRUITS

Oranges	Dates	Strawberries
Grape Fruit	Figs	Blackberries
Bananas	Apples	Raspberries
Peaches	Apricots	Melons
Prunes	Grapes	Tangerines
Pears	Lemons	

NUTS

Hazelnuts	Pecans	Brazil Nuts
Chestnuts	Butternuts	Filberts
Almonds	Pine Nuts	Cocoanuts
Walnuts	Cashew Nuts	

MISCELLANEOUS

Milk	Butter	Olive Oil
Eggs	Olives	Gelatin
Cheese		

May not take:

Meats, fish, fowl, meat soups, meat broths, beef tea, bouillon, kidney, liver, bacon, sweetbreads, peas, beans, string beans, asparagus, mushrooms, oatmeal, shredded biscuit, triscuit, entire wheat bread, tea, coffee, cocoa, chocolate, ale, beer, porter, stout.

Breakfast.—8 oz. milk, 1½ slices bread and 1 pat of butter, 2 tablespoonfuls of cream of wheat with 2 oz. cream and 2 teaspoonfuls of sugar, 1 soft boiled egg.

Dinner.—8 oz. milk, 1 soft boiled egg, potatoes with 1 oz. cream and 1 pat butter, lettuce and cabbage, 1½ slices bread with 1 pat butter.

Supper.—1 egg, 8 oz. milk, 2½ tablespoonfuls of cereal with 1 oz. cream and sugar, crackers with butter, 1 cube of cheese, 1 cup of tea with 1 oz. cream and 1 tablespoonful sugar.

Protein	80 gm.
Fat	112 gm.
Carbohydrate	207 gm.
Calories	2300

Medicinally alkalies are indicated, as they diminish the acidity of the urine and make it a better solvent for the uric acid. The less the acidity of the urine, the greater its content of alkaline phosphates, and, therefore, the greater the quantity of uric acid combined with alkalies, and, therefore, more easily soluble. About 3i potassi. bicarb., either in powder or dissolved in a pint of water, is needed per day. Celestines Vichy, about 1 quart a day, is also of service, on account of its high calcium content. Potassium salts are better than sodium salts, on account of the relative insolubility of the sodium salts.

(c) **Oxalic Acid Calculi.**—It is to be recalled that the condition of the urine most favorable for the solubility of the oxalates should present an increased acidity from the double acid phosphates and an increased content of magnesia with a small amount of calcium. Therefore, we must increase the acidity of the urine, decrease the calcium and increase the magnesium.

The diet should be low in carbohydrates so as to prevent their fermentation, which increases both the formation and absorption of oxalic acid. On account of high oxalate content, the following should be avoided: rhubarb, spinach, sorrel, strawberries, figs, potatoes, beetroot, French beans, tomatoes, plums, tea, coffee and cocoa. Peas, asparagus, mushrooms, onions, lettuce, rice, cauliflower, cabbage, peaches, grapes, apples, carrots, wheat, oats, meat, eggs, butter, milk and sugar may be used. The following is a very efficient diet scheme in oxaluria and related conditions:

DIET SCHEME IN OXALURIA

7:30 a. m.—Glass of hot water.

8:00 a. m.—Fish (haddock, halibut, cod, hake, plaice, mackerel, salmon, trout, etc.), eggs (lightly boiled, poached or scrambled), bacon, ham, chops or steak, stale bread or dry toast with plenty of butter, fruit (apples, oranges, pears, pineapple, peaches, melon).

11:00 a. m.—Glass of water.

1:00 p. m.—Soup (potato, onion, pea, carrot, asparagus), eggs, when not taken at breakfast, chops or steak, cold meat, chicken, tongue, ham, vegetable salads with French dressing, fruit (as at breakfast), a glass of milk or water.

4:00 p. m.—Glass of water.

7:00 p. m.—Raw oysters, soup (as at lunch), fish (as at breakfast), beef, mutton, chicken, vegetables (potatoes, cauliflower, Brussels sprouts, French beans, peas, carrots, lettuce), fruit (as at breakfast), cheese, toast and butter, glass of water.

10:00 p. m.—Glass of hot water.

Note—Take only easily digested vegetables. Avoid too much milk, but take an abundance of water.

Must avoid spinach, sorrel, rhubarb, tomatoes, beets, celery, cucumber, broad beans, haricot beans, grapes, plums, gooseberries, sugar or sweets. Pepper and all condiments and highly seasoned foods. Sweetbreads. Liqueurs and brandy. Figs and gooseberries. Cocoa, tea.

Medicinally acids should be given, for example:

(1) Acidi nitrici diluti ..... ℥ ii
Tinct. cinchonæ comp..... ℥ i
Syr. zingiberis ..... ℥ i
M. et S..... ℥ i t. i. d. p. c.

(2) Acidi lactici..... ℥ i
Tinct. gentianæ..... ℥ ii
Syr. aurantii ..... ℥ iv
Aq. dest. .....q. s. ad ℥ ii
M. et S ..... ℥ i t. i. d. p. c.

(3) Acid sodium phosphate.....gr. xxx t. i. d. p. c.

The magnesia of the urine may be increased by giving magnesium salts or burnt magnesia gr. xxx per day.

Xanthin Calculi

The indications for treatment are the same as those for the treatment of uric acid calculi, tc which it is so closely related chemically.

Cystin Calculi

We know from experimental data that the excretion of cystin is lessened on a low protein intake. For this reason the minimum amount of protein should be used. Klemperer and Jacoby have described a case of cystinuria where the administration of sixteen grams of sodium bicarbonate daily caused the sediment of cystin to disappear from the urine. Smillie has also shown that cystinuria is best treated by a low protein diet with the addition of sufficient alkali to keep the urine alkaline. He found that the addition of sodium bicarbonate did not influence the body metabolism in cystinuria but simply rendered the excreted cystin soluble.

Aminoaciduria, Diaminuria, Peptonuria, Proteosuria, Bence-Jones' Protein, Alkaptonuria and Cystinuria

. . . . . *Jacob Rosenbloom*

Bence-Jones' Protein—Introduction—Does Bence-Jones' Protein Occur in Bone?—Digestive Products of Bence-Jones' Protein—General Chemical Nature of Bence-Jones' Protein—Bence-Jones' Protein in Urine—Bence-Jones' Protein in Blood and Lymph—Proteosuria and Bence-Jones' Protein—Theories Regarding the Origin and the Nature of Bence-Jones' Protein—Possible Derivation from Blood Proteins—Origin from Bone—A Product of Abnormal Metabolism—Metabolism Studies—Bence-Jones' Protein and Multiple Myeloma—Myelopathic Proteosuria (Kahler's Disease)—Treatment—Alkaptonuria—Treatment of Cystinuria.

Aminoaciduria

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Traces of amino acids are normally found in the urine, but under certain pathological conditions they are found in large quantities. As the liver converts amino acids into the urea we should expect that in diseases of the liver there would be an increased urinary excretion of amino acids in the urine. In acute yellow atrophy, phosphorus poisoning, gout, pneumonia, especially during absorption of the exudate, in diabetes and in leukemia the amino acids of the urine are markedly increased.

The following table shows the amounts of amino acid nitrogen found by various investigators:

Author	Amino Acid N, in % of Total Urinary N	Remarks	Reference
Masuda	1-3	Low protein diet	*Z. f. expt. Path. u. Ther.*, 1911, viii, 629.
Masuda	4-5	High protein diet	*Z. f. expt. Path. u. Ther.*, 1911, viii, 629.
Falk & Saxl	1.5-3	Mixed diet	*Z. f. klin. Med.*, 1911, lxxiii, 325.
Signorelli	2	.....	*Bio. Zeit.*, 1912, xxxix, 36; xlvii, 482.
Galambos & Tausz	1.58-4.35	.....	*Z. f. klin. Med.*, 1913, lxxvii, 14.
Van Slyke	1.5-3.5	.....	*J. Biol. Chem.*, 1912, xii, 312; 1913, xvi, 125. *Amer. Jr. Med. Sci.*, 1917, cxliii, 94.
Glaessner	0.5-3.5	.....	*Z. f. expt. Path. u. Ther.*, 1907, iv, 336.
Pfaundler	5-6	.....	*Z. f. physiol. Chem.*, 1900, xxx, 75.
Kruger & Schmidt	5-6	.....	*Z. f. physiol. Chem.*, 1901, xxxi, 556.
Emden & Reese ..	4.32-5.1	.....	*Verh. Cong. f. inn. Med.*, 1905, xx, 304; *Hofmeister's Beiträge*, 1905, vii, 411.
Frey	0.2-0.5	.....	*Z. f. klin. Med.*, 1911, lxxii, 383.
Magnus-Levy	2-6	.....	*Z. f. klin. Med.*, 1911, lxxiii, 325.
Henriques	2.0	Mixed diet	*Z. f. physiol. Chem.*, 1909, lx, 1.

Labbe and Bith found that an increased amino-acid excretion occurs in insufficient amino-acid destruction on the part of the liver, in cases where pathological destruction of proteins is going on, and in conditions of acidosis, whether diabetic or of another nature. Of 40 cases of hepatic disease, all cases which showed a marked injury to the tissues showed an equally marked increase of amino-acid in the urine. Normal values occur in uncomplicated gall-stones and catarrhal jaundice. The same is true in the cases of early Laennec's cirrhosis, but in the later stages of the disease the excretion is increased. Abnormally high values also occur in fatty degeneration, cases of primary tumor, cirrhosis secondary to cardiac disease, and in cases of phosphorus and chloroform poisoning. In cases of marked diabetic acidosis, values of from 0.92 to 3.04 gm. of amino-acid nitrogen per day were found, these values representing 8.4 to 18.4 per cent of the total nitrogen output. In a number of diseases of the gastro-intestinal tract, in gout and chronic rheumatism, normal values were found. In those acute and chronic diseases which are accompanied by an abnormal breaking down of protein tissue, such as occur in the late stages of typhoid, in the crisis of pneumonia and during the absorption of pleuritic and other exudates, in leukemia, etc., constant increased amino-acid excretion was observed in the urine. As a functional test, designed to show the inability of the liver to perform its normal amino-acid decomposition, Labbe and Bith recommend the administration of 20 gm. of peptone while the patient is on a simple milk diet. If under these conditions an increased amino-acid excretion is observed, in all probability this indicates an affection of the liver.

Galambos and Tausz have found an increased excretion of amino acids in diabetes and in diabetic acidosis they found very high values. Löffler and also myself have found the same.

In these cases there is present some defect in the ability of the liver or other tissues to take up these amino acids and for this reason they are excreted.

The presence of the sulphur containing amino-acid cystin will be discussed under cystinuria.

The amino acids tyrosin and leucin were first observed by Frerichs(*g*) as urinary sediments in a case of acute yellow atrophy of the liver. It is to be recalled that these substances have been found in the urine in many diseases such as erysipelas, typhus, typhoid, variola, rabies, leucemia, gout, diabetes, cystinuria, and acute phosphorus poisoning, but are present in solution and not as spontaneously precipitated crystals. They are most often found associated with acute yellow atrophy of the liver, but the crystals have also been found in other conditions. Boston(*d*) found them in a case of jaundice with enlargement of the liver; Kirkbride in a case of erysipelas and osteomalacia; Mann in cases of hepatic congestion due to cardiac disease; Juge in a case of diabetes mellitus with albuminuria;

Ruge in a case of primary carcinoma of the liver; Langstein in a case of jaundice with a stone in the common duct.

Greco found crystals of leucin in the urine in cases of hepatic cirrhosis. Laache and also von Noorden found leucin and tyrosin in cases of pernicious anemia. Smith(*b*) found an abundant sediment of leucin in the urine of a young woman not seriously ill and I have found crystals of tyrosin in the urine of a pregnant patient near term, who passed through a normal delivery and has remained well.

The presence of these amino acids in the urine in cystinuria will be considered under that subject.

The view was formerly held that the appearance of leucin and tyrosin in the urine in cases of grave hepatic disease is due to an inability or diminished ability of the diseased organ to break them down further. However, the fact, which was demonstrated by P. F. Richter(*b*), that they may occur in the urine in cases of acute yellow atrophy in which there is no marked impairment of urea formation and no conspicuous increase of the excreted ammonia, is opposed to such an explanation. Von Noorden suggested that in acute yellow atrophy leucin and tyrosin might be formed in the tissues as a result of bacterial action, whereas the comparatively small amounts excreted in some cases of phosphorus-poisoning might be derived from the intestine. Impaired destructive power of the liver might be regarded as a contributing factor in both conditions.

Since Jacobi showed that leucin and tyrosin are formed abundantly in autolysis of the liver under sterile conditions, it has come to be a very general opinion that their presence in the blood, urine, and liver itself, in cases of acute yellow atrophy and phosphorus-poisoning, is due to the breaking down of the parenchyma of the liver. That in both conditions the hepatic parenchyma undergoes extensive destruction admits of no question.

Diaminuria

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Some subjects of cystinuria excrete certain diamins in the urine. Baumann and von Udransky discovered putrescin, or tetramethylendiamin in the urine of a cystinuric.

$$CH_2 - CH_2.NH_2$$
$$|$$
$$CH_2 - CH_2.NH_2$$ and cadaverin

or pentamethylendiamin.

$$CH_2 - CH_2 - NH_2$$
$$>CH_2$$
$$CH_2 - CH_2 - NH_2$$

These substances may occur together or separately and are also frequently found in the feces and in the intestinal contents.

It has been shown by Ellinger, by feeding experiments that lysin is the mother substance of cadaverin and arginin or ornithin is the mother substance of putrescin.

In severe gastro-intestinal disorders they have also been found in the feces. Neuberg(*l*) gave arginin and lysin to a cystinuric not excreting diamins, and found diamins in the urine but not in the feces. Doubtless diaminuria, like cystinuria, may have an exogenous as well as an endogenous origin. Steyer found that diamins were formed in the autolysis of pancreas and this speaks in favor of the possibility of their origin by the putrefaction of protein.

In cases of intestinal formation of these diamins it is known that bacteria are the producers of these substances, but in cystinuria accompanied by diaminuria the conditions are different In these cases the same metabolic fault is present as leads to the excretion of the cystin, since some of these subjects also excrete other of the primary protein fractions. Both leucin and tyrosin and lysin have been found in cystinuric urines. At times a third diamin seems to occur, the so-called neuridin or saprin, found by Brieger. It may be an isomer of cadaverin but its constitution and its formation are at present unknown.

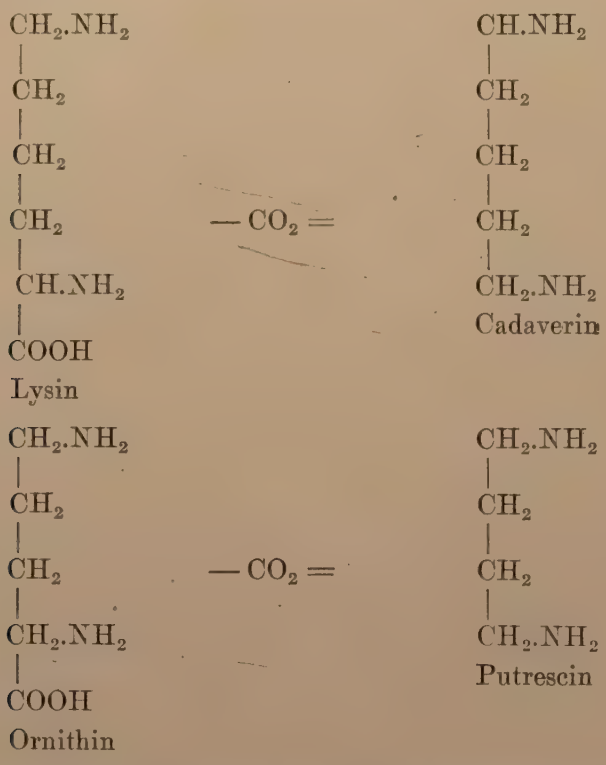
The quantity of diamins excreted is subject to great variations.

Baumann and Udransky isolated 0.2—0.4 gram of diamin of which ⅔ was cadaverin and ⅓ putrescin.

Aside from a notice by Dambrowsky of a trace of pentamethylendiamin in the residue from about 100 liters of normal human urine diamin has never been isolated from the urine, feces or blood of healthy persons.

Brieger has demonstrated the origin of diamin through the action of putrefactive bacteria. Ubiquitous bacteria or specific microörganisms such as cholera germs or the Prior-Finkler bacillus may be responsible. Brieger's discovery was later extended by Ellinger. He determined the particular protein building-stones from which the diamins were produced through transforming lysin into pentamethylendiamin, and arginin, namely its mother substance, diamino-valerianic acid; into tetramethylin, a transformation best made by anaërobic putrefaction. C. Neuberg obtained the diamins, whose synthesis had previously been made by other methods in a simpler manner, by purely chemical means from the appropriate protein cleavage products, namely, by subtraction of carbon dioxid.

The following relations therefore exist between the diamino acids and the diamins:



It is now considered tolerably certain that in the organism, also, both diamins are formed from diamino acids.

Baumann and Udransky's suggestion of an oxidative origin from two molecules of monoamins:

$$2\ CH_3 - CH_2.NH_2 + O = H_2O + \begin{matrix} CH_2 - CH_2.NH_2 \\ | \\ CH_2 - CH_2.NH_2 \end{matrix}$$

is highly improbable, and Garcia's hypothesis that tetramethylendiamin may originate from cystin is absolutely to be discarded.

But whether, in the organism, diamins are always formed from diamino acids in the same manner may be doubted.

In cases of acute intestinal disturbance the responsible bacteria may be considered as producers of the diamins since these bases are metabolism products of microörganisms.

Quite different are the conditions in the diaminuria which occurs in the cystin diathesis. Baumann and Udransky have assumed an intestinal origin for these cases also: cadaverin and putrescin are formed by a chronic intestinal mycosis and through their resorption give rise to cystinuria and diaminuria.

It is probable that cystinuria and genuine diaminuria possess at bottom similar, perhaps identical, causes, namely, various gradual disturbances of protein intermediary metabolism.

Diaminuria and cystinuria have the relation to each other that they represent a group of related disturbances of the normal protein transformation. Both depend on an anomaly in amino acid metabolism. The latter touches most often the sulphur holding, seldomer the basic complexes and at times extends to other cleavage products of protein. That the monoamino acid is excreted as such, the diamino acid after loss of carbon dioxid, after decarboxylization, may have its source in chemical and biological peculiarities of the diamino acids. At all events, decarboxylization is a frequently observed physiological process.

Kossel has found in herring sperm a base, $C_5H_{14}N_4$ named agmatin, which is closely related to the diamins, especially to the tetramethylendiamin.

Apparently it is amino-butylen-guanidin, $NH_2.CH_2 - CH_2 - CH_2 - CH_2.NH - C(:NH) - NH_2$ and according to Kossel has probably come from arginin by splitting off of CO_2 as putrescin comes from $\delta 8$ = diamino-valerianic acid.

We know of no severe artificial derangement of the normal protein metabolism leading to a persistent diaminuria. Diamin feeding may lead to their excretion. Small amounts of these bases are apparently completely oxidized. After giving 3 grams of tetramethylendiamin chlorid to a dog, Baumann and Udransky found 0.056 gram dibenzoyl putrescin in the urine and after giving 10 grams pentamethylendiamin as acetate

they found 0.722 gram of the corresponding dibenzoate in the urine and 0.165 gram in the feces.

Loewy and Neuberg(*a*)(*b*) carried out experiments in which they did not give the poisonous diamins but the corresponding diamino acids to a cystinuria patient. After lysin feeding pentamethylendiamin appeared in the urine, after arginin tetramethylendiamin. Neither base was discoverable in the feces. To be sure, these oral feedings do not exclude that a bacterial origin of the diamins from the diamino acids takes place in the digestive canal. Formation through microörganisms is, however, quite improbable in view of the fact that their long observed case of cystinuria had hitherto proceeded without diaminuria.

According to all appearances, diaminuria is like cystinuria a constitutional anomaly to which no significance pertains. That, however, does not hold without qualification for the formation of diamins through the special action of bacteria. The diamins are not altogether innocuous (Pohl) and as Pohl(*c*) has also shown it is to be remembered that certain syntheses, such as the formation of paired glycuronic acids and of hippuric acid may be inhibited through diamins. Contrary to the old assumption of Baumann and Udransky, the form in which diamins appear in the body, whether as free bases or as salts, appears to be without significance (Roos(*a*)(*b*)).

It is to be recommended that future investigations should distinguish strictly between chronic excretion of bases and the diaminuria caused by infectious diseases. Also that they should be observant of properties which might pertain to pyrazin, to spermin and to the base of the Leyden-Charcot crystals (Kikkoji and Neuberg).

Diaminuria is harmless and has no practical clinical significance. It presents no symptoms and is diagnosed only by the chemical isolation of the substances from the urine and feces.

Peptonuria and Proteosuria

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Peptonuria

Peptones, the last stage in the digestion of protein before the amino acids are produced, are rarely if ever found in the urine. Some have claimed to have found them present together with proteose in pneumonia, pulmonary tuberculosis, ulcer of the stomach and in women during the puerperal period. In these cases, however, there are reasons to believe that the substance present was not true peptone but was some type of proteose.

At present the condition presents nothing of clinical or therapeutic interest.

Proteosuria

Both primary (protalbumose and heteroalbumose) and secondary (deuteroalbumose) proteoses may be present in urine. They may occur alone or associated with protein. The following distinct types of this condition may be noted:

1. Pyogenic: found in conditions associated with presence of pus in the system, due to the dissolution of the pus cells and absorption of the digested protein substance of the pus cells. It is observed in pneumonia during the stage of resolution, in gangrenous conditions, in empyema, bronchiectasis, abscess formation and in meningococcus infections.

2. Hepatogenous: found in cases of marked disturbance in liver function such as acute yellow atrophy, phosphorus poisoning, carcinoma, cirrhosis and catarrhal jaundice.

3. Enterogenous: found in cases of gastric and intestinal ulceration and no doubt due to the breaking down of tissues.

4. Hematogenous: found in scurvy, leukemia, purpura, dermatitis, hemolytic poisons, pregnancy, dead fetus, psychoses and cancer, no doubt brought about by the toxins.

5. Febrile: found in all fevers due to the toxins of the disease and to the septic processes associated with the disease.

6. Digestive or alimentary: following the ingestion of large amounts of proteoses possibly due to an ulcerative condition some place along the digestive tract, or due in part at least to pathological conditions in the kidney. Pollak(*b*) has suggested that these cases should be called "renal proteosuria."

7. Mixed albuminuria of Senator: in these cases the proteose is present in the urine, together with protein, and is specially prominent in cases of nephritis, notably the syphilitic type.

From the metabolic and therapeutic standpoint nothing further need be said about this condition at the present time.

Bence-Jones' Protein

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I. Introduction

In 1847 Bence-Jones presented before the Royal Society of London a paper "On a New Substance Occurring in the Urine of a Patient with Mollities Ossium," in which he described, for the first time, the substance since known as the Bence-Jones' protein. Later he described several properties of this substance, and gave the results of a study of it in his report on mollities ossium. Ebstein (*Zeit. f. Urol.,* 1915, IX, 208) has pointed out that Heller described this substance before Bence-Jones'. The Bence-Jones' protein was rediscovered and described by Kuehne in 1869. It has since been the subject of many investigations, especially by Matthes, Ellinger, Magnus-Levy, Jochman and Schumm, Bradshaw, Moffat and Simon. Anders and Boston have tabulated all the known cases of multiple myeloma and Bence-Jones' proteinuria with the characteristics of each up to 1903, and reported three new cases. Weber recorded 28 cases prior to 1904 and gave the histories of 10 more cases. Moffat recorded 39 cases prior to 1905 and Permin recorded 40 cases up to 1907. Decastello(*b*) in a recent paper described two more cases and made an analysis of those previously recorded. Martiri has compiled 204 cases and reports one new case. Magnus-Levy(*f*), and also Grutternick and deGraaf, and recently Walters have succeeded in obtaining Bence-Jones' protein in crystalline form.

Does Bence-Jones' Protein Occur in Bone?—Ellinger(*b*) succeeded in obtaining Bence-Jones' protein in small amounts from diseased bone-marrow. Hopkins and Savory could not find the substance in the bone-marrow from the cases they studied. Virchow found it in the bone-marrow in cases of osteomalacia, so-called. Barr could not find in the bone-marrow substance of the bone tumor any trace of Bence-Jones' protein or of enzymes. Wood claims to have separated Bence-Jones' protein from a portion of bone affected by multiple myeloma, but could not obtain it from the bone-marrow in any other portion of the body of the patient. Askanazy was able to demonstrate its presence in the bone-marrow of a case of multiple myeloma, but was unable to find it in blood from this patient. Lowery could not detect a trace of Bence-Jones' protein in the marrow of the affected ribs and humerus of Kalischer's case. Weber,

however, was able to prove the presence of a substance giving reactions similar to those of Bence-Jones' protein, in the vertebræ and ends of the femur in a case of multiple myeloma, but he could not detect this substance in any other tissue or organ. Bruce, Lund, and Whitcomb found, in a case of multiple myeloma, that the fluid obtained from an affected bone, after sawing through it, gave the reaction of the Bence-Jones' protein. Ribbinik could not find Bence-Jones' protein in the bone-marrow substance of the case studied by him. Fleischer(*b*), however, has found a substance giving the reaction of Bence-Jones' protein in normal bone-marrow. In a case of Weber's, microscopic section of some of the organs and the new growth in multiple myeloma showed the presence of a homogeneous hyaline substance which he thought might possibly be Bence-Jones' protein. Bradshaw and Warrington, in an analysis of a rib affected with multiple myeloma, found the relation of organic and inorganic substances to be practically normal.

Digestive Products of Bence-Jones' Protein.—Moitessier on subjecting Bence-Jones' protein to gastric digestion obtained metaprotein, primary proteose (except heteroproteose), secondary proteose and peptone. After peptic digestion of Bence-Jones' protein, Simon could not detect primary proteose among the products formed, but found deuteroproteose "B" (Pick) and peptone "A" (Pick). Coriat found Bence-Jones' protein digestible in artificial pancreatic juice.

General Chemical Nature of Bence-Jones' Protein.—Magnus-Levy published results of a study of the digestive products of Bence-Jones' protein, its reactions and contents of amid, diamino and monoamino nitrogen. Huppert recorded results of various elementary analyses that have been made of Bence-Jones' protein. Abderhalden and Rostoski made an analysis of Bence-Jones' protein to determine the amounts of the various amino acids contained. Hopkins and Savory found that Bence-Jones' protein yields all the amino acids characteristic of typical protein, and that it contains a large proportion of aromatic radicals.

Reach gave the results of an analysis of Bence-Jones' protein in terms of its nitrogen partition. Gross and Allard(*a*) administered 10 gm. of Bence-Jones' protein to an alkaptonuric subject, with otherwise unaltered diet. There was a large increase in the output of homogentisic acid, which suggested to them that Bence-Jones' protein is rich in aromatic radicals.

Bence-Jones' Protein in Urine.—Zuelzer(*b*) obtained Bence-Jones' protein in the urine of dogs poisoned with pyrodin (monoacetylphenylhydrazin), a strong hemolytic agent. Stokvis found Bence-Jones' protein in the urine of dogs after its intravenous or rectal injection. Matthes also found it in the urine of a dog after the subcutaneous injection of Bence-Jones' protein. Ellinger introduced 5 gm. of Bence-Jones' protein intravenously into a dog, but the urine yielded no precipitate with

$(NH_4)_2SO_4$, although the liquid gave a strong biuret reaction suggestive of peptone (Kuehne), which may have been derived from the injected material. I have studied a case in which the Bence-Jones' protein was spontaneously precipitated from the urine.

Allard and Weber and Decastello have found that the roentgen ray treatment of the bone tumor had no effect on the urinary output of Bence-Jones' protein. Walters has recently found that radium exposure over two femoral masses caused no reduction in the amount of Bence-Jones protein excreted in the 64 days following the exposure. Voit and Salvendi reported a case in which diet appeared to modify the elimination of Bence-Jones' protein, but Weber observed that changes of diet had no influence on its elimination in his case of multiple myeloma. Hopkins and Savory found that the amount of excreted Bence-Jones' protein was proportional to the extent of metabolism rather than to any other factor. Massini claimed that the amount of the Bence-Jones' protein excreted was proportional to the amount of the protein of the food. Walters found that the quantity of Bence-Jones' protein excreted is independent of the protein intake and the amount of the protein excreted during the night when food is not taken is only slightly less than the amount excreted during the day. He claims that there is not a constant relationship between the amount of Bence-Jones' protein excreted and the total urinary nitrogen excreted.

Bence-Jones' Protein in Blood and Lymph.—Ribbinik and Askanazy could not find Bence-Jones' protein in the blood of patients with multiple myeloma. Ellinger obtained it from ascitic fluid. Coriat found Bence-Jones' protein in a pleural effusion from a patient suffering from multiple neuritis associated with extreme tenderness of the ribs, although the protein was absent from the urine. Rostoski found that the method of "precipitin" detection fails to distinguish Bence-Jones' protein from various proteins of human origin. Donati and Satta have shown that serum albumin, serum globulin, edestin, egg albumin, milk and milk serum, inhibit the hemolytic action of sodium glycocholate and sodium oleate, whereas ovo-albumin, Bence-Jones' protein and casein accelerate the hemolysis. Borchart and Lippmann found that after feeding Bence-Jones' protein to fasting dogs, it could be detected in serum from the animals by the precipitin test and in samples of their blood by chemical tests. Abderhalden has lately isolated the protein from the blood of a patient with multiple myeloma.

II. Proteosuria and Bence-Jones' Protein

Proteoses have been found in the urine under many conditions, usually in minute quantities and as temporary constituents of the urine during the course of specific fevers, inflammatory processes, and other diseases. The urinary proteoses present different characteristics from those of

Bence-Jones' protein, however, and must be sharply distinguished from the latter. Among the most prominent of these differences between Bence-Jones' protein and ordinary proteoses, the following may be indicated in the terms of Bence-Jones' protein:

1. Soluble in water (different from heteroproteose).
2. Coagulated at low temperature (unlike other proteose collectively), through elastoses are precipitated by heating their aqueous solution but redissolve as the temperature falls.
3. Convertible into metaproteins (unlike other proteose collectively).
4. Digested by pepsin-HCl, yields protoproteose (unlike all proteoses).
5. Not acted upon by erepsin (different from proteoses).
6. Excreted in larger proportions than the proteoses.
7. Does not dialyze through parchment paper (different from all soluble proteoses).
8. Not precipitated from saline solution by dialysis (different from several proteoses).
9. Capable of producing anaphylaxis.

III. Theories Regarding the Origin and the Nature of Bence-Jones' Protein

Proteose Relationships.—Kuehne believed that Bence-Jones' protein is closely related to heteroproteose on account of the fact that the pure substance, after its precipitation from its solution by heating, redissolves with further elevation of the temperature. Huppert also thinks the protein is heteroproteose. Dechaunne considers it a mixture of at least three proteins or groups of proteins, probably proto- and dysprotcoses, and a substance like heteroproteose. Kuehne and Chittenden found that on the basis of elementary composition, Bence-Jones' protein resembled heteroglobulose. Neumeister showed that Bence-Jones' protein is not heteroproteose. He did not believe that there is any relation between digestive conditions and the presence of this substance in the urine. He thought rather, that it is a substance of a peculiar kind and quite unlike any other that had hitherto been described. Matthes was of the same opinion as Neumeister.

Possible Derivation from Blood Proteins.—Simon thinks Bence-Jones' protein is formed from the serum globulins, perhaps by an enzymotic action of the tumor cells, and that once produced, it is rapidly excreted by the kidneys as are all foreign proteins. Kuehne and Chittenden suggest that it may arise from serum globulin. Coriat also thinks it might be formed from serum globulin. He supposes it is produced by the digestive action of leucocytes or bacteria, or, more particularly, by the enzymotic action of plasma cells in the bone-marrow. Moitessier(*a*)(*b*) believed that

Bence-Jones' protein is derived from blood proteins under the influence of the new bone growth. Lindemann concluded that, while Bence-Jones' protein cannot be put in any present group of proteins, it is nearest in relationships to the true proteins. Abderhalden stated that, judging from its yield of amino acids, Benco-Jones' protein does not correspond to either of the two serum proteins, but may be considered a tissue protein, which, without being broken down or changed into one of the serum proteins, is transmitted to the blood and is then probably eliminated as an protein foreign to the blood. Schultz suggested that the Bence-Jones' protein might prove to be related to globin.

Origin from Bone.—Donetti believes that Bence-Jones' protein results from some loss of function of the bone-marrow, owing to the destruction of the latter. Hopkins and Savory concluded that it is formed by processes that indicate interruptions in the normal autolytic processes in tissues due to toxin from the growth. They also suppose that the loss of some normal function of the bone-marrow may give rise to Bence-Jones' protein. Weber and Hutchinson concluded that Bence-Jones' protein is formed from granules in the myelomatous cells. Virchow believed the substance resulted from degenerative changes in protein occurring in sarcomata. Weber also thought it may be due to an abnormal metabolic or degenerative process in the myelocytes, or in the tumor cells derived from the myelocytes or their predecessors. Von Rustizky likewise considered that the substance is produced in connection with new bone growth. Williams thought that Bence-Jones' protein may represent modified glycoproteins from disorganized bones and tendons. He accounts for the variable properties of Bence-Jones' protein products by assuming that the glycoproteins are more or less broken up and then excreted in different degrees of chemical decomposition according to the stage of the disease. In a recent paper Weber and Ledgingham suggested, from the histological evidence in the case of multiple myeloma studied by them, that the cytoplasmic residues of karyolyzed plasma cells may be the source of Bence-Jones' protein. Abderhalden by means of his "optical method" has found that the serum from a patient excreting the Bence-Jones' protein digested all the organs of the patient, but not those of another individual. The serum also digested the urinary protein and he thinks the positive results are due to the digestion of the Bence-Jones' protein which is infiltrating all the organs.

Ottenberg and Gies have found that crude elastose, after its subcutaneous or intraperitoneal injection, can readily be detected in the urine by the heat precipitation test. Since Bence-Jones' protein has various properties in common with elastoses, Ottenberg and Gies suggested that osseoalbumoid (bone elastin?) might be the forerunner of Bence-Jones' protein.

Several years ago, I endeavored to determine whether osseoalbumoid might be so acted upon by the enzymes present in cells of myelomatous growths as to give rise to a substance having the properties of Bence-

Jones' protein. The result of that investigation suggested that Bence-Jones' protein may be formed from osseoalbumoid by the action of enzymes present in bone-marrow.

A Product of Abnormal Metabolism.—Senator inclined to the view that the Bence-Jones' protein represents a product of the abnormal metabolism of food protein. Magnus-Levy also thought it was formed from food proteins as a result of alter protein metabolism. As much as 30 to 79 gm. of Bence-Jones' protein may be excreted per day, whereas the total amount of protein in all the tumor tissue seldom exceeds, or indeed equals, this quantity. Magnus-Levy considers it impossible for so much urinary protein to arise from so little tumor tissue. Rostoski advanced the same view. Hopkins and Savory concluded, from studies of metabolism and effects of diet, that Bence-Jones' protein is a product of endogenous metabolism.

It is possible that multiple myeloma is due to a specific infectious agent, which by the action of its toxins so alters the normal changes occurring in the bone-marrow as to produce this substance from the tissue proteins. This idea is strengthened by the analogy Weber has drawn between the characteristics of multiple myeloma and mycosis fungoides, which is thought by some to belong to the group of infective granulomata. This view is stimulated by the fact that in the case studied by Weber and Ledingham the growth consisted of plasma cells. The sarcoma-like tumors of the skin, known as mycosis fungoides, have been found to be plasmomata. Another idea that might be held as to its mode of formation is the follow-

TABLE I. LOW PROTEIN DIET.

URINARY NITROGEN

Date, Jan.	19-20	20-21	21-22	22-23	23-24	24-25
Volume, c.c.	2040	1370	1700	1960	1540	1630
Sp. gr.	1.0120	1.0125	1.0110	1.0105	1.0110	1.0110
Bence-Jones' protein, gm.	2.61	2.66	2.80	1.76	1.96	2.77
Total N. gm.	8.36	6.61	6.10	5.70	5.51	5.00
Total non-protein N. gm.	7.95	6.19	5.66	5.44	5.19	4.56
Protein N. gm.	0.41	0.42	0.44	0.26	0.31	0.44
Urea N. gm.	6.29	4.97	4.00	3.77	3.76	3.40
Ammonia N. gm.	0.43	0.36	0.61	0.35	0.35	0.21
Creatinin N. gm.	0.45	0.39	0.37	0.37	0.39	0.35
Creatin N. gm.	0	0	0	0	0	0
Uric acid N. gm.	0.16	0.13	0.19	0.15	0.13	0.13
Rest N. gm.	0.62	0.34	0.51	0.63	0.56	0.47
PER CENT IN TOTAL NITROGEN						
Protein	4.8	6.3	7.2	4.5	5.6	8.8
Urea	79.1	75.3	65.5	69.4	68.2	68.0
Ammonia	5.2	5.8	10.8	6.4	6.7	4.6
Creatinin	5.3	5.9	6.0	6.4	7.0	7.0
Creatin	0	0	0	0	0	0
Uric acid	1.8	1.9	3.1	2.6	2.3	2.6
Rest	7.4	5.1	8.3	10.1	10.1	9.4

ing: Possibly the columnar epithelium that lines the alimentary canal is diseased. The agent that converts the digestive products may therefore fail to function. In consequence, the incompletely synthesized products are taken into the blood stream and then eliminated as a matter foreign to it. Abderhalden and Rostoski have shown that Bence-Jones' protein yields a "precipitin" which is active with human serum. It must therefore represent assimilated material and cannot be an exogenous product derived directly from intestinal processes.

IV. Metabolism Studies

Folin and Denis(*g*) report the following metabolic findings in a case excreting Bence-Jones' protein. The patient during this experiment was kept on a *low* protein diet. (See Table I, page 490.)

When the patient was given a *high* protein diet the following results were obtained. They decided that "there is nothing like a definite or constant relationship between the total nitrogen and the protein of the urine. Allard and Weber also found no relationship between the amounts of protein catabolized and the Bence-Jones' protein eliminated.

TABLE II. HIGH PROTEIN DIET

Date, Jan.	25-26	26-27	27-28	28-29	29-30	30-31	31-Feb. 1	Feb. 1-2
Volume, c.c.	1190	1310	1600	1150	1050	1300	1140	1570
Sp. gr.	1.018	1.021	1.016	1.022	1.025	1.025	1.029	1.025
Bence-Jones', protein, gm.	3.70	5.45	4.39	6.33	5.54	6.10	6.04	5.00
Total N. gm.	6.57	8.72	9.40	11.50	13.10	15.62	15.71	16.60
Total non-protein N. gm.	5.92	7.85	8.70	10.49	12.22	14.65	14.75	15.80
Protein N. gm.	0.59	0.87	0.70	1.01	0.88	0.97	0.96	0.80
Urea N. gm.	3.81	6.17	6.85	7.68	10.17	10.59	11.76	12.80
Ammonia N. gm.	0.79	0.43	0.57	1.03	0.73	0.72	0.78	0.86
Creatinin N. gm.	0.33	0.33	0.28	0.37	0.35	0.29	0.31	0.39
Creatin N. gm.	0.04	0.08	0.12	0.05	0.04	0.14	0.08	0
Uric acid N. gm.	0.14	0.13	0.15	0.14	0.13	0.14	0.15	0.16
Rest N. gm.	0.80	0.62	0.73	1.22	0.80	1.75	1.66	1.60
PER CENT OF TOTAL NITROGEN								
Protein	9.0	10.0	9.3	8.8	6.7	6.2	6.1	4.8
Urea	58.6	70.9	73.0	66.7	77.6	74.1	74.9	77.1
Ammonia	13.3	5.5	6.8	9.9	5.9	4.9	5.3	5.1
Creatinin	5.0	3.7	2.8	3.2	2.6	1.8	1.9	2.3
Creatin	0.6	0.9	1.2	0.4	0.3	1.0	0.5	0
Uric acid	2.1	1.4	1.5	1.2	1.0	0.9	0.9	0.9
Rest	12.1	7.1	7.6	10.4	6.1	11.2	10.5	9.6

These observers also found that the amount of the Bence-Jones' protein excreted was constant in the day and night urines as is shown in the following table:

TABLE III

Day	Time	Volume	Total Nitrogen	Bence-Jones' Protein
			grams	grams
1	Day	500	9.7	2.9
	Night	260		2.3
2	Day	350	9.2	2.5
	Night	360		2.5
3	Day	360	9.9	2.6
	Night	300		1.7
4	Day	315	10.3	2.0
	Night	370		3.1
5	Day	330	8.0	2.0
	Night	320		2.7
6	Day	340	6.8	2.3
	Night	320		2.7

Hopkins and Savory in the following interesting table report studies on a case of multiple myeloma excreting the Bence-Jones' protein.

TABLE IV

Date 1905	Urine c.c.	Total N. per diem	Protein per 100 c.c.	Protein per diem	Protein-N. per diem	Non-protein-N. per diem	Pr. N. x 100 / Tot. N.	Diet, etc.
March 23	868	....	1.65	14.32	2.32	....	....	Uncontrolled diet.
25	1092	8.66	1.22	13.32	2.15	6.51	26.9	" "
26	1148	8.93	1.26	14.46	2.34	6.59	26.2	" "
27	1145	6.62	1.05	12.02	1.95	4.67	30.0	Milk diet.
Apr. 1	1092	7.69	1.13	12.34	2.00	5.69	26.0	Uncontrolled diet.
3	1274	8.42	0.890	11.34	1.84	6.58	21.8	" "
5	1232	6.63	0.850	10.47	1.70	4.93	25.6	Second day of a gelatin diet.
May 4	1344	....	0.780	10.48	1.70	....	....	Uncontrolled diet.
6	1064	6.34	1.00	10.64	1.72	4.62	27.1	" "
8	896	7.47	1.32	11.83	1.92	5.55	25.7	Protein in diet intentionally increased.
9	1120	9.98	1.06	11.87	1.92	8.06	19.3	
10	1125	8.70	1.16	13.05	2.11	6.59	24.2	
11	1008	6.49	1.16	11.69	1.89	4.60	29.0	Uncontrolled diet.
12	952	5.80	0.96	10.30	1.67	4.13	28.8	Bone-marrow administered and continued for one week.
13	1400	7.69	0.820	11.48	1.86	5.83	24.2	Uncontrolled diet.
14	1680	9.64	0.670	11.29	1.83	5.81	24.0	
15	1400	8.11	0.610	8.54	1.38	6.73	17.0	
16	1512	6.39	0.640	9.67	1.57	4.82	24.5	
20	1624	....	0.995	16.16	2.62	....	....	Day following cessation of bone-marrow.
22	1680	....	0.620	10.42	1.69	....	....	.....
23	1624	8.31	0.757	12.09	1.96	6.35	23.5	Ordinary diet.
25	1792	5.94	0.547	10.80	1.75	4.19	29.5	Second day of gelatin diet.
26	1465	7.11	0.732	11.48	1.86	5.25	26.0	Ordinary diet.
27	1008	7.08	1.10	11.05	1.79	5.29	25.2	" "
28	672	6.52	1.79	12.03	1.95	4.57	30.0	" "

TABLE IV—(*Continued*)

Date		Urine c.c.	Total N. per diem	Protein per 100 c.c.	Protein per diem	Protein-N. per diem	Non-protein-N. per diem	Pr. N. x 100 / Tot. N.	Diet, etc.
1905									
	29	728	7.28	1.74	12.66	2.04	5.24	28.0	Ordinary diet.
	30	728	....	1.52	11.06	....	....	....	" "
	31	1120	....	0.97	10.83	....	....	....	" "
June	13	1120	7.34	0.850	9.52	1.54	5.80	20.9	" "
	15	1120	7.84	0.970	10.76	1.73	6.11	22.0	" "
	17	1400	9.50	0.822	11.50	1.86	7.64	19.5	1 lb. of beef per diem added to ordinary diet.
	18	1344	11.32	0.922	12.39	2.01	9.31	17.7	
	19	1512	11.54	0.782	11.82	1.91	9.63	16.5	
	20	1624	11.97	0.857	13.96	2.26	9.71	18.9	Uncontrolled diet.
	21	1064	7.97	1.125	11.97	1.94	6.03	24.3	" "
	22	1465	6.85	0.702	10.19	1.65	5.20	24.1	" "
July	18	1176	6.50	0.763	8.97	1.45	5.05	22.3	" "
	21	1064	8.22	1.185	12.61	2.04	6.18	24.8	" "
Aug.	12	1120	6.57	0.867	9.71	1.57	5.00	23.9	" "
	15	1064	7.97	1.185	12.92	2.09	5.88	26.2	" "
	18	1120	....	1.005	11.26	1.82	....	....	" "
	22	1120	6.94	0.822	9.21	1.49	5.45	21.4	" "
Nov.	3	952	....	1.11	10.57	1.71	....	....	" "
	5	1120	9.12	1.06	11.87	1.92	7.20	21.0	15 gm. pancreatic digestion product of casein.
	6	1120	7.55	0.922	10.33	1.67	5.88	22.4	Uncontrolled diet.
1906									
May	29	740	10.06	1.100	8.14	1.32	8.74	13.0	Beginning of nine days period in which the N-balance was estimated.
	30	850	11.47	0.932	7.92	1.28	10.19	11.1	
	31	1090	11.23	0.741	8.08	1.31	9.92	11.7	
June	1	1030	13.00	0.814	8.39	1.36	7.03	10.4	
	2	1523	14.30	0.591	9.01	1.46	12.84	10.0	
	3	1072	12.72	0.744	7.98	1.29	11.43	10.1	
	4	902	9.00	0.797	7.19	1.16	7.84	12.9	
	5	846	10.18	0.942	7.97	1.29	8.89	12.6	Witte's peptone (20 gm.) formed part of the diet.
	6	846	10.11	0.944	7.99	1.29	8.82	12.7	End of balance period.
	25	896	....	0.975	8.73	1.41	....	....	Uncontrolled diet.
	29	1512	....	0.565	8.54	1.38	....	....	4th and 5th days of a rigid vegetarian diet.
	30	1344	....	0.600	8.06	1.30	....	....	Ordinary diet.
July	1	840	....	0.910	7.64	1.24	....	....	After 3 days of bone-marrow.
	6	336	....	2.800	9.50	1.54	....	....	Ordinary diet.
	7	392	....	2.050	8.04	1.30	....	....	" "
Nov.	14	...	....	.....	7.80	....	....	....	" "
	20	...	....	.....	8.29	....	....	....	" "
Dec.	9	...	....	.....	7.84	....	....	....	
1907									
Oct.	13	840	6.43	1.582	13.30	2.15	4.28	33.3	Uncontrolled diet.
	14	928	7.08	2.147	15.65	2.53	4.55	35.7	" "
	15	952	7.69	1.560	14.85	2.40	5.69	31.2	" "
	18	672	6.12	1.800	12.11	1.96	4.16	32.0	" "
1908									
Jan.	14	616	7.81	.....	.....	....	....	....	" "
	15	560	6.80	2.740	15.34	2.48	4.32	36.5	" "
	16	504	8.21	3.537	18.24	2.95	5.26	35.6	
1909									
Jan.	24	420	5.54	0.802	3.37	0.546	5.00	10.0	Day immediately preceding death.

In tables Nos. V, VI, and VII, they present the data in their study of the metabolism of three different cases excreting the Bence-Jones' protein:

TABLE V

Case B Date 1907	Urine c.c.	Total N. per diem	Protein per 100 c.c.	Protein per diem	Protein-N. per diem	Non protein-N. per diem	Pr. N. × 100 / Tot. N.	Diet, etc.
April 26	1755	23.30	2.24	39.30	6.40	16.90	27.5	Uncontrolled.
27	1698	22.58	2.40	40.75	6.64	15.94	28.5	"
28	1472	19.89	2.31	35.00	5.70	14.19	28.7	"
29	1754	21.41	2.09	36.68	5.98	15.43	28.0	"
30	2207	24.50	1.85	40.83	6.65	17.85	27.5	"
May 1	1811	24.09	2.12	38.39	6.26	17.83	26.0	"
Case C 1910								
Jan. 15-20 mixed sample	.....	.....	2.73	.....	.....	.....	30.4	"
Feb. 23	1460	12.26	1.67	24.38	3.97	8.29	32.4	Flesh.
25	1600	12.64	1.47	23.52	3.83	8.81	30.3	Milk.
April 16	1195	10.54	1.73	20.67	3.37	7.17	32.0	Milk and fish.
17	1130	11.94	2.08	23.50	3.83	8.11	32.0	Flesh.

TABLE VI

Date 1906	N. in Food gms.	N. in Urine gms.	N. in Feces gms.	Total N. Excretion gms.	Balance N. gms.
May 29	15.86	10.06	0.65	10.71	+ 5.15
30	13.32	11.47	"	12.12	+ 1.20
31	13.67	11.23	"	11.88	+ 1.79
June 1	14.39	13.00	"	13.65	+ 0.74
2	13.76	14.30	"	14.95	— 1.19
3	12.88	12.72	"	13.37	— 0.49
4	9.45	9.00	"	9.65	— 0.20
5	13.77 *	10.18	"	10.83	+ 2.94
6	11.84	10.11	"	10.76	+ 1.08
Total for 9 days	118.94	102.07	5.85	107.92	+ 11.02
Average per diem ...	13.21	11.34	0.65	11.99	+ 1.22

* Witte's peptone (19.7 gm., containing 3.33 gm. nitrogen) formed part of the total ingesta on this occasion.

TABLE VII

Case and Date	Total Non-protein N.	N. as Urea	Urea N. in Percentage of Non-protein N.	Method of Urea Estimation
A. 1905				
April 3	6.58	4.80	73	Morner-Sjoquist
5	4.93	3.70	75	"
May 28	4.57	3.12	70	"
July 1-10 Mixed sample of 10 days	5.20	3.90	75	Folin
B. 1907				
April 30	17.85	17.07	90	Morner-Sjoquist
May 1	17.83	16.22	91	"
C. 1910				
Feb. 23	8.29	6.68	80	"
25	8.81	7.20	82	"

Case and Date	Preformed Creatinin p. d.	Total Creatinin	Creatin Estimated as Creatinin
A. 1908			
Jan. 14	0.542	0.769	0.227
15	0.425	0.649	0.224
16	0.534	1.360	0.826
B. 1909			
April 26	1.690		
27	1.555		
28	1.270		
29	1.270		
30	1.440		
May 1	1.470		
C. 1910			
Feb. 23	0.847	1.460	0.613
25	0.840	1.451	0.611
April 16	0.968	1.220	0.252
17	1.096	1.412	0.316

The above excretion of creatin was not associated with acidosis. At no time were acetone substances detected in the urine.

Blatherwick has studied the calcium metabolism in a case of multiple myeloma and found it at a higher plane than normal. He found that the absorption of calcium was active as shown by the partial retention of calcium when calcium lactate was added to the diet. He concluded that as a result of the osseous lesions a liberation of calcium has taken place which is shown by an increased excretion. Williams in two days found 0.92 gm. and 1 gm. calcium in the urine of his patients, which represent high values.

Seegelken has reported the following findings in a case of multiple myeloma excreting Bence-Jones' protein.

The patient was on the following diet, Table No. VIII, during this time and the metabolic findings are shown in Table No. X.

TABLE VIII

	Grams	Nitrogen	Fat	Carbohydrate	Calories
Meat	80	2.72	0.72	.....	76.0
Ham	50	2.10	1.80	.....	70.5
Wheat Flour	200	2.60	2.00	120.0	582.0
Eggs	80	1.75	8.72	.....	126.3
Butter	60	0.06	52.20	0.3	488.4
Cocoa	20	0.62	6.32	8.0	107.4
Sugar	10	....	.....	10.0	41.0
Milk	400	2.00	12.0	18.0	236.0
Meat Soup	500	0.35	7.5	25.0	170.0
		12.20	91.26	181.3	1897.6

TABLE IX

	Urine								Feces			
Body-Weight	Volume c.c.	Sp. Gr.	Total—N	Urea	Purin-bases	CaO	P_2O_5	NaCl	N	CaO	P_2O_5	NaCl
51.5	2250	1010	10.9170	8.5146	1.0115	0.3524	1.9025	8.072				
51.5	2500	1012	10.5700	9.1421	0.9842	0.3383	1.8750	8.102				
51.7	2045	1010	10.7046	9.0136	1.1632	0.3121	1.9203	7.272				
51.5	2380	1013	10.1959	8.3212	1.2421	0.2942	2.0230	7.950				
51.5	2165	1012	10.0023	8.5124	0.9624	0.2894	1.7969	7.153	1.3214	1.1910	1.2656	0
51.5	2210	1012	10.5196	8.7231	1.0200	0.3146	1.7941	6.565				
51.5	2425	1013	10.4566	9.1421	0.8422	0.3511	1.9061	5.466		pro	die	
51.7	2570	1010	10.4642	8.4923	1.1076	0.2844	1.9456	6.021				
51.8	2335	1012	9.6108	7.9262	1.2622	0.2912	1.8248	5.230				
51.5	2000	1013	10.7100	9.9410	0.9466	0.3244	1.8396	4.922				

Walters has recently obtained the following results in metabolic studies of three cases of multiple myeloma excreting Bence-Jones' protein, Tables X, XI, and XII.

TABLE X

EXCRETION OF BENCE-JONES' PROTEIN DURING THREE-HOUR INTERVALS IN CASE 2

	General Diet					
	9/18/20 to 9/19/20		9/19/20 to 9/20/20		9/20/20 to 9/21/20	
Hours	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.
8 p.m. to 8 a.m.	1,375	1.02	860	1.33	450	4.9
8 a.m. to 11 a.m.	385	0.25	320	0.70	219	0.47
11 a.m. to 2 p.m.	160	0.15	350	0.77	186	0.46
2 p.m. to 5 p.m.	255	0.32	...	....	35	0.07
5 p.m. to 8 p.m.	340	0.51	310	0.88	218	0.26
Total	2,515	2.25	1,840	3.68	1,108	6.16
Total night		1.02		1.33		4.9
Total day		1.23		2.35		1.26

TABLE XI

EXCRETION OF BENCE-JONES' PROTEIN DURING THREE-HOUR INTERVALS IN CASE 1

	General Diet																	
	8/31/20 to 9/1/20		9/1/20 to 9/2/20		9/2/20 to 9/3/20		9/3/20 to 9/4/20		9/4/20 to 9/5/20		9/5/20 to 9/6/20		9/6/20 to 9/7/20		9/7/20 to 9/8/20		9/8/20 to 9/9/20	
Hours	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein gm.
8. p.m. to 8. a.m.	1,455	10.43	640	6.46	1,150	8.72	1,150	8.26	1,050	8.19	675	2.39	850	17.85	845	9.21	995	9.36
8 a.m. to 11 a.m.	228	2.02	360	2.38	95	2.10	210	1.21	460	6.51	225	1.77	255	0.58	325	2.28	100	2.04
11 a.m. to 2 p.m.	380	2.48	375	1.89	120	2.13	250	2.31	400	2.30	200	1.37	235	2.12	360	2.72	125	2.18
2 p.m. to 5 p.m.	230	2.61	240	2.07	128	2.20	165	2.56	175	0.65	170	3.61	440	0.17	160	3.75	305	3.05
5 p.m. to 8 p.m.	129	1.34	305	2.24	161	5.21	250	2.54	135	5.03	180	1.72	250	3.55	180	2.88	122	2.27
Total.....	2,422	18.88	1,910	15.04	1,654	20.36	2,025	16.88	2,220	22.68	1,450	10.86	2,030	24.27	1,870	20.74	1,647	18.90
Total night..		10.43		6.46		8.72		8.26		8.19		2.39		17.85		9.21		9.36
Total day...		8.45		9.58		11.64		8.62		14.49		8.47		6.42		11.53		9.54

	Nonprotein Diet												High Protein Diet					
	9/9 to 9/10		9/10 to 9/11		9/11 to 9/12		9/12 to 9/13		9/13 to 9/14		9/14 to 9/15		9/15 to 9/16		9/16 to 9/17		9/17 to 9/18		9/18 to 9/19	
	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein gm.
8 p.m. to 8 a.m.	810	8.19	910	7.32	750	7.56	1,210	20.14	840	6.72	895	5.83	960	3.93	1,010	8.41	900	6.54	890	9.71
8 a.m. to 11 a.m.	50	0.98	240	1.98	205	1.78	190	1.62	150	2.11	75	2.13	95	2.99	100	2.67	205	2.03	300	3.25
11 a.m. to 2 p.m.	178	2.71	280	2.20	125	1.94	130	2.34	130	2.12	130	1.91	120	1.79	280	1.74	150	2.10	215	2.04
2 p.m. to 5 p.m.	250	2.29	240	2.13	450	2.22	450	1.54	130	1.51	160	2.13	230	1.92	300	2.54	350	1.96	310	2.76
5 p.m. to 8 p.m.	190	2.38	140	1.50	280	2.10	245	2.48	190	2.08	120	2.28	190	1.21	100	1.89	130	2.75	120	1.75
Total.....	1,478	16.55	1,810	15.13	1,810	15.60	2,225	28.12	1,440	14.54	1,370	14.28	1,595	11.84	1,390	17.25	1,735	15.38	1,835	19.51
Total night..		8.19		7.32		7.56		20.14		6.72		5.83		3.93		8.31		6.54		9.71
Total day ..		8.36		7.81		8.04		7.98		7.82		8.45		7.91		8.84		8.84		9.80

TABLE XII

EXCRETION OF BENCE-JONES' PROTEIN DURING TWELVE-HOUR INTERVALS IN CASE 3

		Total Nitrogen, Gm.	Protein Gm.	Diet
11/ 9/20	8 a.m. to 8 p.m.	2.4	5.4	Milk
	8 p.m. to 8 a.m.	6.3	8.45	
11/10/20	8 a.m. to 8 p.m.	5.0	7.8	Milk
	8 p.m. to 8 a.m.	2.0	4.79	
11/11/20	8 a.m. to 8 p.m.	3.3	7.4	Milk
	8 p.m. to 8 a.m.	4.4	7.3	
11/12/20	8 a.m. to 8 p.m.	3.0	6.9	General
	8 p.m. to 8 a.m.	3.8	9.44	
11/13/20	8 a.m. to 8 p.m.	—	—	—
	8 p.m. to 8 a.m.	—	—	—
11/14/20	8 a.m. to 8 p.m.	1.7	10.5	Mosenthal
	8 p.m. to 8 a.m.	1.5	3.87	
11/15/20	8 a.m. to 8 p.m.	3.8	9.3	General
	8 p.m. to 8 a.m.	2.2	5.7	
11/16/20	8 a.m. to 8 p.m.	2.0	9.1	General
	8 p.m. to 8 a.m.	2.0	5.76	
11/17/20	8 a.m. to 8 p.m.	2.4	2.4	General
	8 p.m. to 8 a.m.	4.4	8.25	
11/18/20	8 a.m. to 8 p.m.	—	—	General
	8 p.m. to 8 a.m.	3.7	6.67	
11/19/20	8 a.m. to 8 p.m.	3.9	7.0	Starvation
	8 p.m. to 8 a.m.	2.7	5.07	
11/20/20	8 a.m. to 8 p.m.	—	—	—
	8 p.m. to 8 a.m.	—	—	
11/21/20	8 a.m. to 8 p.m.	2.7	5.73	General
	8 p.m. to 8 a.m.	3.2	7.07	
11/22/20	8 a.m. to 8 p.m.	6.3	18.5	General
	8 p.m. to 8 a.m.	3.0	2.34	
11/23/20	8 a.m. to 8 p.m.	4.7	6.04	General
	8 p.m. to 8 a.m.	5.2	6.04	

V. Bence-Jones' Protein and Multiple Myeloma

Myelopathic Proteosuria (Kahler's Disease).—In 1889 Kahler and Huppert reported a case of multiple myeloma from clinical and chemical standpoints, respectively, and in 1897 Bozzola reported a case under the title of "Sulla Malattia di Kahler," thus recognizing Kahler as the first to show the relationship between proteosuria (so-called) and primary bone disease. The lesions, however, were classified in 1873 as myeloma by von Rustizky.

Careful study of cases of Bence-Jones' proteinuria shows that there must certainly be some relation between the excretion of Bence-Jones' protein and diseased conditions of the bones. Although we cannot say that Bence-Jones' protein is peculiar to the growth known as multiple myeloma,[1] it is certain that Bence-Jones' protein is present in the urine in 80

[1] Various names applied to multiple myeloma: Myeloma multiplex (Rustizky), sarcoma multiplex ossium (Buch), pseudoleucemia myelogenes (Runeberg), osteo-

per cent of the cases exhibiting this condition. In cases of excretion of Bence-Jones' protein unaccompanied by multiple myeloma disease of the blood-forming organs or of bone have been present.

Weinberger found Bence-Jones' protein in urine from a case of chloroma; Vidal from a case of tuberculous osteoarthritis; Kahler from primary lymphosarcoma of the spinal cord; Oerum from a case whose bone tumors were multiple metastases of a gastric carinoma. The case of osteomalacia which was reported by Jochman and Schumm was subsequently shown to be one of multiple myeloma, and that of Askanazy, reported as one of lymphatic leukemia, was undoubtedly one of multiple myeloma. Fitz described a case of myxedema excreting the Bence-Jones' protein. Miller and Baetjer, cases of nephritis excreting this protein.

Decastello has reported four cases of leukemia associated with Bence-Jones' proteinuria. Collins reported a case of undoubted multiple myeloma that was observed for several months and in which there was no excretion of Bence-Jones' protein. Naunyn reported a case in which the whole skeleton was riddled with metastatic carcinomatous growths, without the presence of Bence-Jones' protein bodies in the urine. Boggs and Gutherie have reported four cases of leukemia and one case of metastatic carcinoma in which the Bence-Jones' protein was excreted in the urine. Scheele and Herxheimer reported a case of multiple myeloma with no Bence-Jones' protein in the urine.

The above-mentioned case of Naunyn's may be explained, according to Weber, as follows: The tumor cells derived from bone-marrow cells, however much they may resemble morphologically true bone-marrow cells, are prone to abnormality (including unusual degenerative changes) than real myelocytes. Furthermore, metastatic tumors in the bone-marrow do not give rise to Bence-Jones' protein for the reason that non-myelogenic tumor cells are not affected in the same way.

The view of Decastello that Bence-Jones' protein is excreted only by individuals with diseased kidneys is hard to reconcile with the statement of some that the serum proteins are never, and by others that they are seldom excreted with Bence-Jones' protein. One would think that if the kidneys are diseased, albuminuria would occur in a larger proportion of cases. Bence-Jones' protein is excreted in 80 per cent of the cases of multiple myeloma, but it does not appear likely that so many would present kidney lesions. It seems more probable that the kidney lesions result from the excretion of Bence-Jones' protein rather than that they cause its elimination, especially since Stokvis has shown that hemiproteose after its subcutaneous injection passes through the kidneys without doing them any

myelitis maligna (Grawitz), osteosis sarcomatosa (Hammer), endothelioma intravascular (Markwald), lymphosarcoma multiplex ossium (Wieland), myelosarcoma (Schmaus), lymphadenia ossium (Nothnagel), erythroblastoma (Ribbert), plasmoma malignum (Hoffman).

apparent injury. If such injections are repeated frequently, however, the excreted hemiproteose excites organic disease in the kidneys.

VI. Treatment

As regards the treatment of this condition, the only possibility is by use of the roentgen ray. Decastello has lately advised in conjunction with this the use of benzol on the following basis. He thinks that the Bence-Jones body originates in the bone marrow, and hence is not influenced by the peripheral raying. The administration of benzol might reach it in the bone marrow, and it has been shown by Boggs and Guthrie that under benzol treatment the amount of Bence-Jones' protein excreted in the urine of leukemic patients is reduced.

Alkaptonuria

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NEW YORK

Nature sometimes betrays her workings in her playful moods. It is as if she tires of perpetually keeping her mysteries dark, and slightly opens the veil for us to glance and see her exquisite, complicated methods. We glance and are much instructed, guessing what we cannot perceive and sometimes constructing a whole scientific philosophy of the mechanisms of life. Such an insight into the catabolic processes of the human being is obtained by the study of the inborn error of metabolism known as alkaptonuria.

The condition is a very rare one and altogether unfraught with danger. The patient comes complaining that he stains his laundry black, or he becomes frightened, should he be an observant individual at the coal black hue that his urine assumes upon standing. Or it may be that he is rejected for insurance, because the examiner found a reducing substance in the urine. It is true that the reduction of Fehling solution is not as typical as the one obtained with glucose; nor is the bismuth in Nylander's solution reduced, although darkening occurs. This urine upon being treated with an alkali will turn intensely black. It is this affinity for alkalies that has won for it the name of alkapton. The urine does not turn the polarized ray of light, nor does it ferment. With ferric chlorid an intense blue color is obtained.

Garrod, in his Croonian lectures, pointed out that this disturbance was noted long ago. In the books of Scribonius (1584), of Schenk (1609), and of Lusitanus (1649) instances are described of patients who suffered with the anomaly of micturating black urine. In 1823, Alexander Marcet(*b*) reported the case of an infant whose urine became darker on standing, turned black with alkalies, and stained the napkins and linens.

One would think from the evidence at hand that alkaptonuria is a Mendelian recessive character. According to Garrod, who has collected the instances of alkaptonuria in certain families, the figures, though not accurately corresponding to the Mendelian law, still show a close relationship to it, while Bateson and Punnett are convinced that alkaptonuria is a rare recessive character in the Mendelian sense.

It seems that a considerable number of the alkaptonuric individuals are the children of first cousin marriages (Garrod). That does not mean that marriage of first cousins tends to alkaptonuria, but the presence of a recessive characteristic in both of the parents will, of course, intensify the production of the recessive characteristic in the offspring. The following table shows that in eight consanguineous marriages there were fifteen alkaptonuric individuals, whereas in ten families where the parents were not blood relations there were only nineteen alkaptonuric members:

Families the Offsprings of First Cousins

	Names of Observers	Number of Alkaptonuric Members
1.	Pavy	4
2.	R. Kirk	3
3.	Garrod	2
4.	Erich Meyer	1
5.	Ogden	1
6.	Hammarsten	2
7.	Grutterink and van der Bergh	1
8.	Cronvall	1
	Number of families, 8	15

Families of Parents Who Were Not Blood Relations

	Names of Observers	Number of Alkaptonuric Members
1.	W. Smith and Garrod	2
2.	Ewald Stier	1
3.	Nocciola and Domenici	1
4.	Marshall and Futcher	3
5.	Langstein and E. Meyer	1
6.	Garrod and T. W. Clarke	1
7.	Grutterink and van der Bergh	2
8.	Grutterink and van der Bergh	4
9.	Schumm	1
10.	Fromherz	ω
	Number of families, 10	19[1]

[1] In some instances private information has supplemented the published records. (Garrod.)

	Observers	Total Number in Family	Normal Members	Alkaptonuric Members
Family No. 1	F. W. Pavy	14	10	4
" 2	Fromherz	12	9	3
" 3	Nocciola and Domenici	10	9	1
" 4	Ogden	8	7	1
" 5	Zimper	8	6	2
" 6	Winternitz	7	4	3
" 7	Langstein and E. Meyer	6	5	1
" 8	Schumm	6	4	2
" 9	Garrod	5	3	2
" 10	R. Kirk	4	1	3
" 11	Bandel	4	2	2
" 12	Hammersten	4	2	2
" 13	W. Smith and Garrod	3	1	2
" 14	Baumann and Embden	2	0	2
" 15	Ewald Stier	2	1	1
" 16	Erich Meyer	1	0	1
" 17	Garrod and Clarke	2	1	1
" 18	Cronvall	1	0	1
Totals		99	65	34

Debenedetti has recently described a family where no instances of alkaptonuria were known until two cousins married. Four sons of this marriage all had alkaptonuria. The two daughters escaped.

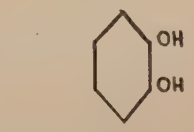
The anomaly is chronic and persists throughout life in those patients who were thoroughly investigated and whose histories are authentic. It seems more common in males than in females. There are those who have reported alkaptonuria of a transitory nature in patients suffering from other diseases. Zimnicki reported a case of intermittent alkaptonuria in a patient who had hypertrophic cirrhosis of the liver; Geyger in a case of diabetes; Slosse in a pyonephritic individual, von Moraczewski(*a*) in a case of tuberculosis, and C. Hirsch in a girl 17 years of age who for three days passed an alkapton urine while suffering from a febrile gastro-enteritis.

To Boedeker(*a*)(1859) is due the honor of naming the anomaly here discussed and describing its characteristics. It was Marshall, however, who in 1887, isolated the alkapton substance from the urine and called it glycosuric acid. Previous to Marshall, Ebstein and Müller in 1875 found in the urine of a child pyrocatechol which they thought was the alkapton substance of Boedeker. A urine containing pyrocatechol will turn dark if exposed to the air, especially if the reaction is alkaline. It will also reduce copper solutions.

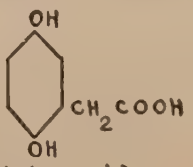
Fleischer and Smith ascribed the alkapton properties of the urine to protocatechinic acid. Before coming to the actual substance found in the urine of alkaptonurics, we wish to dismiss with a few words the question of the presence of uroleucic acid in the urine of alkaptonurics. Kirk(*a*) described in 1886 a substance which he isolated from urine of alkaptonuric patients. This substance melted at 133.3° C., whereas homogentisic acid melts at 146-147° C. While the results of Kirk were confirmed by Huppert and by Langstein and Meyer, Garrod and Hurtley, reviewing the entire subject critically, deny the existence of such a substance in the urine. In fact, Kirk expressed the opinion that his so-called "uroleucic" acid was impure homogentisic acid. It is curious to note that Hurtley, in translating Carl Neuberg's chapter on the "Rarer Disturbances of Protein Metabolism," makes no mention of the conclusion of the absence of such a substance as uroleucic acid, and states: "In addition, a second aromatic dioxy acid found by Kirk is also occasionally present."

It was, however, in 1891 that Wolkow and Baumann isolated homogentisic acid from a case of alkaptonuria. This acid crystallizes with 1 molecule of water in large, transparent, prismatic crystals, which lose their transparency with the loss of the water of crystallization. They melt at 146.5-147° C. They are soluble in water, alcohol, ether, and nearly insoluble in chloroform and benzene. With Millon's reagent, the acid gives a lemon colored precipitate, reduces Fehling's, is optically inactive and is non-fermentable. With benzoyl chlorid and sodium hydroxid in the presence of ammonia, Orton and Garrod obtained the amid of dibenzoylhomogentistic acid, which melts at 204° C., a reac-

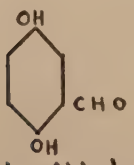
tion which is of value in the detection and isolation of the substance from the urine. The lead salt melts at 214-215° C. (Hammarsten.)



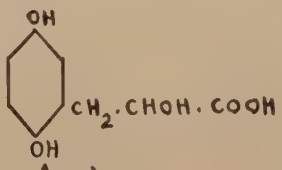
Pyrocatechol



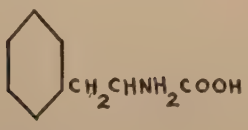
Homogentisic acid
(alkapton; glycosuric acid)



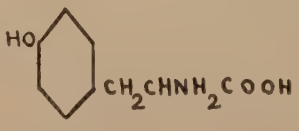
Gentisic Aldehyde



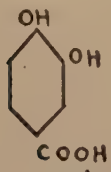
Uroleucic Acid



Phenylalanin

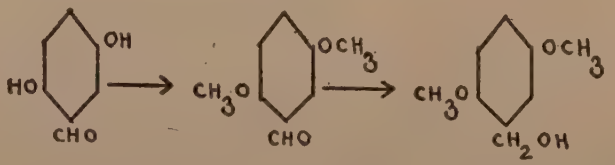


Tyrosine

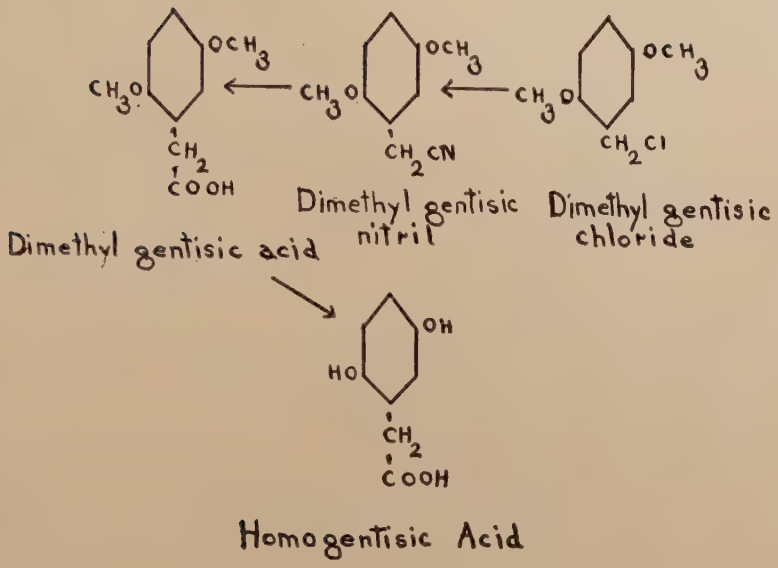


Proto-catechinic acid

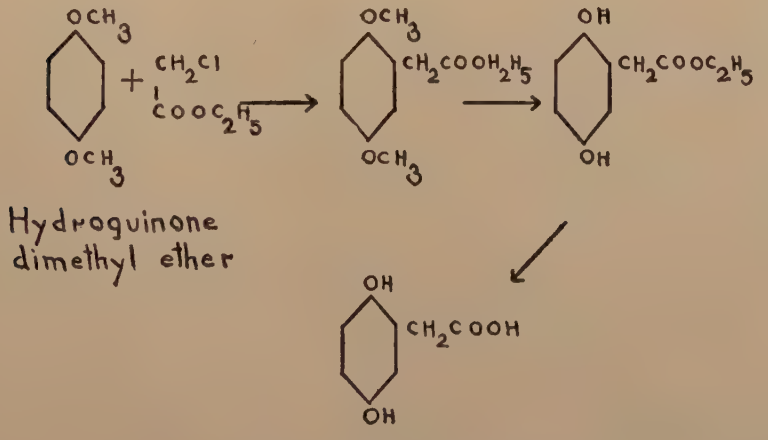
That homogentisic acid has the formula ascribed to it above is proven by the fact that three methods for its synthesis demonstrate its constitution. Baumann and Frankel were the first to prepare it artificially from gentisic aldehyde (1-4-dioxybenzaldehyd):



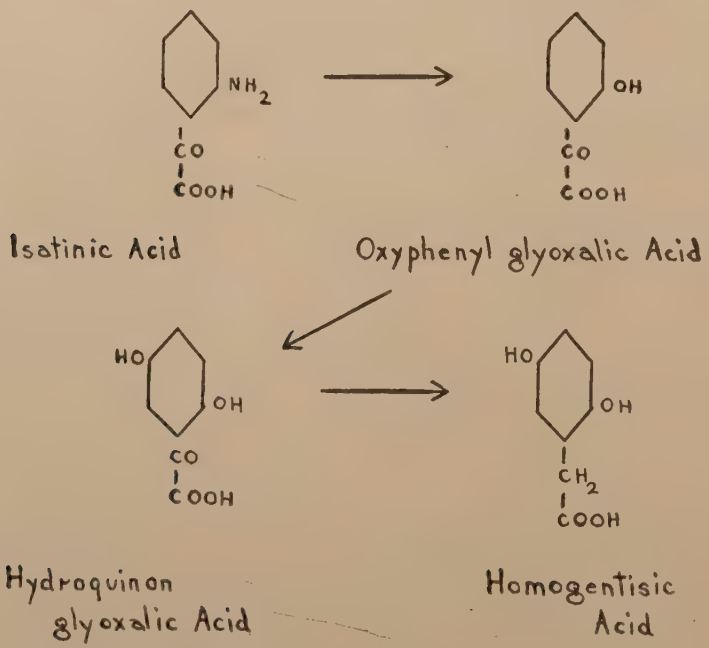
Gentisic aldehyde | Dimethyl gentisic aldehyde | Dimethyl gentisic alcohol



Osborne synthesized homogentisic acid by condensing hydroquinone dimethyl ether with ethyl monochloracetate in carbon disulphid solution by means of aluminium chlorid and removing the methyl groups from the resulting ether by amorphous phosphorus and hydriodic acid:



Another method of its synthesis is from isatinic acid, as described by Neubauer and Falta:



The formation of alkapton in the body was first investigated by Baumann and Wolkow. They had surmised that the aromatic fraction of the protein molecule was responsible for the formation of homogentisic acid. Upon feeding an alkaptonuric with 10 grams of tyrosin, they obtained a yield of 7.5 grams of alkapton in the urine, that is, over eighty per cent of the theoretically possible quantity. An even larger excretion (93.5 per cent) of homogentisic acid was obtained by Mittelbach after the feeding of tyrosin.

That it was the protein in the food that was responsible for the alkapton was demonstrated by Ogden and by Stange, who showed that a pure protein diet increased the homogentisic acid from 25 to almost 50 per cent above a mixed diet.

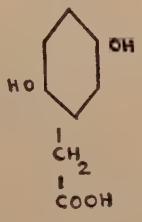
Not only tyrosin, but a number of other compounds have been shown to cause the formation of homogentisic acid.

We have enumerated in the accompanying table the alkapton formers, in alkaptonuric subjects, and those substances which do not yield alkapton.

Alkapton Formers	Do Not Form Alkapton
1. Phenylalanin.	1. Benzoic acid.
2. β-phenyl- α-oxypropionic acid.	2. Phenyl acetic acid.
3. Phenyl pyrotartaric acid.	3. Phenyl propionic acid.
4. Tyrosin.	4. Cinnamic acid.
5. p-hydroxy- m-amino- phenylalanin.	5. Phenyl glyceric acid.
6. p-oxy-phenyl pyrotartaric acid.	6. Phenyl-β-oxypropionic acid.
7. Hydroquinon pyrotartaric acid.	7. Phenyl amino-acetic acid.
	8. α-phenyl α-amino-butyric acid.
	9. Phenyl-ethylalcohol.
	10. o-oxyphenyl acetic acid.
	11. m-oxyphenyl acetic acid.
	12. p-oxyphenyl acetic acid.
	13. p-oxyphenyl propionic acid.
	14. o-coumaric acid.
	15. coumarin.
	16. p-coumaric acid.
	17. o-oxyphenyl pyrotartaric acid.
	18. m-oxyphenyl pyrotartaric acid.
	19. o-oxyphenyl lactic acid.
	20. m-oxyphenyl lactic acid.
	21. p-oxyphenyl lactic acid.
	22. o-tyrosin.
	23. m-tyrosin.
	24. 3.5 dibrom-tyrosin.
	25. 3.5 diiodo-tyrosin.
	26. Caffeic acid.
	27. Tryptophan.
	28. Gentisic acid.
	29. Protocatechinic acid.
	30. 2.4 dioxybenzoic acid.

It was a difficult matter for Wolkow and Baumann to explain the transformation of tyrosin to homogentisic acid.

Tyrosin



Homogentisic acid

In the tyrosin molecule the OH group is one and in the para position, whereas in the alkapton molecule the OH groups are two, one in the ortho and one in the meta position. Since they knew of similar changes produced by bacteria in other instances, Wolkow and Baumann suggested that

tyrosin of the food protein is changed by the intestinal bacteria into homogentisic acid. This explanation, however, met with severe criticism, and Baumann's pupil, Embden, was the first to cast aspersion on its validity. The objection to the intestinal bacterial origin of alkapton may be summarized as follows:

1. It is impossible to influence the excretion of alkapton by means of intestinal disinfectants. (Embden.)

2. No organism can be grown from the feces that is capable of transforming tyrosin into the homogentisic acid. (Embden.)

3. Fasting an alkaptonuric individual shows that the alkapton is derived not only from the food protein, but also from the catabolism of the tissue protein. This was first demonstrated by Mittelbach. He found that on a full diet an alkaptonuric excreted 4.66 grams alkapton, whereas during starvation he still excreted 2.57 grams of this substance.

4. Abstinence from protein food, while it diminishes, does not arrest the elimination of the homogentisic acid in an alkaptonuric. (Langstein and Meyer.)

5. It was demonstrated by Abderhalden, Bloch and Rona that the parenteral administration of glycyl-l tyrosin caused an increase in the alkapton excretion, in which case surely the intestinal flora could have had no effect.

6. Feeding proteins poor in tyrosin did not influence the alkapton excretion in the urine, showing that the tyrosin in the alimentary canal was not the only aromatic compound that is changed to homogentisic acid. (Falta.)

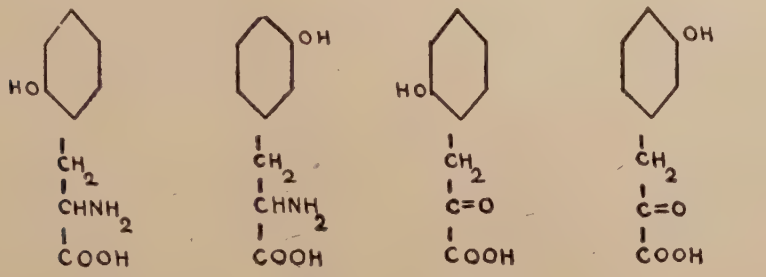
7. Should the intestine thus change the tyrosin and the phenyl alanin before absorption, the tissue protein of alkaptonurics should exhibit a deficiency of these aromatic amino acids, seeing that they are not synthesized in the animal organism. Abderhalden and Falta, who have analyzed the blood proteins as well as the proteins of the hair and nails of alkaptonuric subjects, have not found any deviation from the normal.

How then is the homogentisic acid formed? If one will glance at the list of alkapton formers enumerated previously, one will see that they have all of the following properties in common (Neuberg):

1. They are aromatic acids.
2. They have a three membered side chain.
3. The side chain can undergo substitution in the α-position.
4. The substitution products may be α-amino, α-oxy, or α-keto acids.
5. The benzol ring must either be unaltered, or
6. The benzol ring may undergo substitution in the para position alone or in the 2-5 position simultaneously.

It was found by Blum that orthotyrosin and metatyrosin did not influence the excretion of alkapton. Not only is this the case for the

o- and m-tyrosin, but also for the ortho- and metaoxyphenyl pyruvic acid, according to Neubauer.

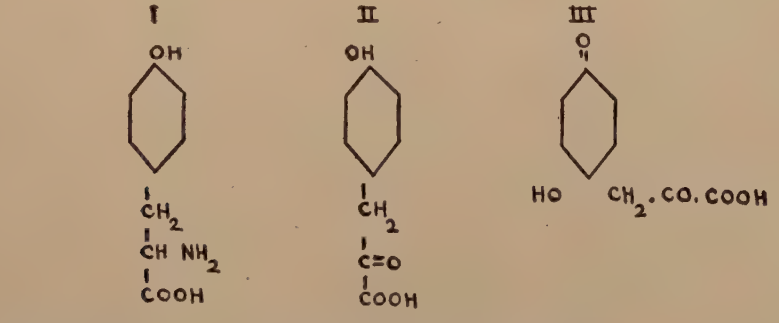


o-tyrosin m-tyrosin o-pyruvic acid m-pyruvic acid

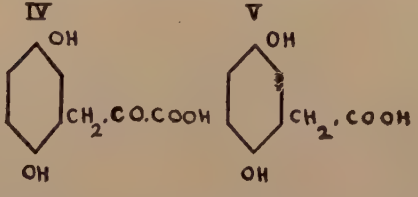
The paratyrosin and the parapyruvic acid will influence the alkapton excretion.

It was Erich Meyer(*a*) who first suggested that the para-oxy group is rather a necessity in the change from p-tyrosin to alkapton, and that the change takes place by a shifting of the side chain rather than by a movement of the OH radicals.

Neubauer suggested that the transformation of the α-amino acids in the body takes place through an intermediary α-ketone acid as follows:



p. Tyrosin p-oxy-phenylpyruvic acid



Hydroquinone pyruvic acid Homogentisic acid

That this is the path of the change is further confirmed by the fact that the feeding of hydroquinon pyruvic acid (IV) augments the amount of alkapton excreted in the urine.

In 1892, Garnier and Voirin advanced the hypothesis that the disturbance in alkaptonurics is a failure to break down the homogentisic molecule. According to their view, this molecule is produced in the normal metabolism of protein, but whereas in the normal individual the molecule is broken down, in the alkaptonuric the homogentisic acid is excreted unchanged. To this view the modern trend of opinion seems to tend. The arguments in support of it are as follows:

1. Were homogentisic acid an abnormal intermediary product, the body would use measures to protect itself against it. This acid is not excreted combined with sulphuric or glycuronic acid, but is excreted as its ammonium salt unchanged in the urine. With an abnormal constituent like gentisic acid, its homologue, Likhatscheff, has shown that it is excreted when administered as the aromatic sulphate.

2. The administration of homogentisic acid to normal individuals in fairly large quantities fails to cause its overflow into the urine. That is, it is completely broken down. If very large quantities are administered traces of it are found in the urine (Embden).

3. That the power to catabolize homogentisic acid is completely lost in the alkaptonuric, and not simply overtaxed, is shown by the fact that not part but all of the tyrosin and phenylalanin fraction of the broken down protein is changed to alkapton and is excreted as such in the urine.

Knoop and Grutterink and van den Bergh have, however, raised certain objections to the above hypothesis, and it is rather difficult to pass them by without some discussion.

It is known that in dogs the power to catabolize homogentisic acid is limited. Knoop, therefore, administered to dogs phenyl-α-lactic acid, which in alkaptonurics increases the output of alkapton. In the dogs no excretion of the alkapton was observed.

Similarly in individuals suffering from hepatic disease and diabetes, the Dutch authors found an inability properly to burn homogentisic acid. To such subjects they administered tyrosin in doses of 10 to 15 grams. No appearance of alkapton in the urine was observed after such tyrosin administration.

Dakin's experiments, referred to later, also seem to indicate that formation of homogentisic acid is always pathological.

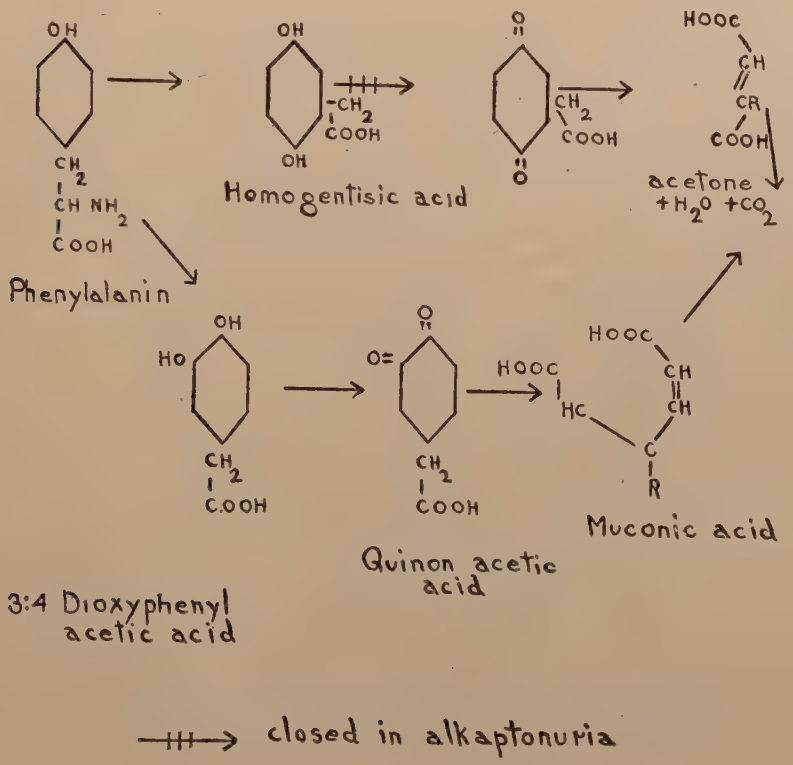
It would seem, as Garrod points out, that "the most serious objection which can be raised to the view that homogentisic acid is an abnormal product, peculiar to alkaptonurics, is that such a view involves the assumption that the alkaptonuric, who alone has the power of forming homogentisic acid, is also exceptional in having no power of destroying it when formed."

The amount of homogentisic acid excreted bears a definite ratio to the total nitrogen output, depending entirely on the diet taken. This Garrod has demonstrated to be the fact by compiling such a table of statistics from the experiments of several observers. It appears that a quantity of any given protein will, in an alkaptonuric, tend to form and excrete a definite amount of the alkapton substance, that amount being the maximal one.

There is reason for belief that the anomaly in function responsible for the failure to break down the alkapton is lodged in the liver, for in normal livers perfusion of homogentisic acid causes it to be broken down to acetone (Embden).

This, however, requires much further experimentation.

Fromherz and Hermanns believe that the aromatic amino acids normally follow a dual path to destruction and that in alkaptonuria one of the paths is closed. They present the mechanism as follows:



Neubauer and Falta emphasized the idea that homogentisic acid is always formed in normal metabolism, but in alkaptonurics it cannot be oxidized as they have lost the power to split the benzol ring.

TABLE SHOWING THE DAILY H : N[1] RATIOS IN FIVE CASES OF ALKAPTONURIA, DURING PERIODS IN WHICH MIXED DIETS WERE TAKEN

Anton M., in Basle, Aged 50 Years				Male 20 Years O. Schumm	Thomas P., Aged Eight Years		Albert P., Aged Four Years	Minnie L., Aged Three Years
Langstein and E. Meyer		Falta						
46 : 100	36 : 100	48.1 : 100	40.0 : 100	44.5 : 100	43.8 : 100	44.1 : 100	48.4 : 100	42.7 : 100
44 "	42 "	44.9 "	38.0 "	42.2 "	39.9 "	48.1 "	47.6 "	27.0 "
42 "	38 "	40.3 "	40.5 "	47.6 "	35.9 "	44.7 "	44.9 "	48.3 "
42 "	34 "	44.3 "	40.8 "	42.6 "	40.0 "	49.0 "	52.7 "	39.6 "
43 "	34 "	50.4 "	41.1 "	49.5 "	37.7 "	.....	48.8 "	39.1 "
46 "	40 "	44.5 "	.....	42.9 "	44.4 "	.....	50.7 "	34.5 "
46 "	53 "	40.9 "	.....	45.8 "	35.9 "	.....	45.4 "	44.8 "
44 "	40 "	40.8 "	.....	41.3 "	38.7 "	.....	54.3 "	.....
.....	45 "	41.8 "	.....	.....	43.9 "	.....	53.5 "	.....
.....	54 "	... "	.....	.....	.....	.....	.....	.....
Averages:—								
44 : 100	41.6 : 100	44.0 : 100	40.1 : 100	44.0 : 100	40.0 : 100	46.5 : 100	49.6 : 100	39.4 : 100

[1] H : N = homogentisic acid : nitrogen.

However, Dakin gave to alkaptonurics paramethylphenylalanin $CH_3C_6H_4CH_2CHNH_2COOH$ and paramethoxyphenylalanin $CH_3OC_6H_4$-CH_2CHNH_2COOH and has found that they were oxidized in the organism. He concludes that the formation of homogentisic acid in metabolism is always pathological and that the benzol ring can be broken even in alkaptonuria.

Abderhalden and Bloch gave a fixed diet to a person suffering from alkaptonuria and on one of the days of the experiment gave him 5 liters of water. Their results were as follows:

Diet	*N Balance*	*N in Urine*	*Homogentisic Acid*
	gm.	*gm.*	*gm.*
Normal food	+1.36	18.2	10.52
Normal + 5 L. water	—2.19	21.75	10.18
Normal food	+1.47	18.09	10.27

They believe that this constancy of the output of homogentisic acid indicates a constancy of protein metabolism throughout.

Falta fed alkaptonurics with pure protein and found that casein yields most alkapton. The following table shows the amounts of homogentisic acid excreted upon feeding the various proteins:

Protein	Amount of Protein Added to Normal Diet Gms.	Increase in the N Excretion Gms.	Increase in the Homogentisic Acid Excretion Gms.	H : N	100 gm. Protein Yield Homog. Acid Gms.	Calculated Amount
Casein	60	7.75	4.22	54.6 : 100	8.7	7.23
	80	10.81	5.58	51.6 : 100	8.3	
Fibrin	50	4 ?	2 ?	50.? : 100	8.0 ?	....
	82	11.52	5.94	51. : 100	8.26	
Oxyhemoglobin	82	8.45	3.71	43.9 : 100	7.0	5.5
Blood globulin	50	7.42	2.85	37.1 : 100	5.93	....
	80	11.34	4.06	35.8 : 100	5.73	
Serum albumin	50	7.5 ?	3.0 ?	40. : 100	6.4 ?	5.0
	82	10.11	3.51	34.7 : 100	5.5	
Ovalbumin	80	10.42	2.56	24.7 : 100	3.7	2.5
	82	11.39	2.37	21.0 : 100	3.15	
Gelatin	..	.....	....	.....	....	2.5

Katsch has lately tabulated the metabolic findings in a case of alkaptonuria in a boy who has been under observation and the subject of research for several years. He found that the alkaptonuria subsides dur-

ing the acidosis produced by the withdrawal of carbohydrates. When the acidosis supplants the alkaptonuria, the amount of acetone bodies eliminated is larger than can be explained by the transformation of the aromatic protein complexes.

There is a distinct relationship between alkaptonuria and ochronosis. That there are cases of ochronosis without alkaptonuria has also been definitely shown. Out of 25 cases of ochronosis collected from the literature by Poulsen(*b*)(1910), 12 were alkaptonuric, 2 showed phenol in the urine, 2 had melanin in the urine, 6 patients had normal urine and in 3 the urine findings were not recorded.

It was in 1866 that Virchow(*c*) first described ochronosis. While performing the autopsy on a man who had died of an aneurysm, he noticed that all the cartilages were black, "black as ink," or "as if they had been immersed in ink." All the cartilages showed signs of progressive hypertrophy, and the pigmentation was ascribed by Virchow to a hematin pigment.

It was Albrecht and Zdarek who in 1902 pointed out that ochronosis may be due to alkaptonuria, and Osler two years later described the development of this pigmentation in two cases of alkaptonuria. Further testimony was advanced by Clemens, Wagner, Gross and Allard, Landois, Poulsen, Söderbergh, Janney and others.

It is not, however, only the cartilages that may be stained by the homogentisic acid. In alkaptonuria, the cerumen may be stained dark brown (Bandel). Stier also found the aural wax brown. While the alkapton has not been found in sweat, the sebaceous glands secreted colored, greenish substances which contained alkapton. Abderhalden and his co-workers found homogentisic acid in the blood of an alkaptonuric.

While it is the general opinion that alkaptonuria is a harmless perversion of metabolism, Umber seems to think that it may lead to arthritic disease, to osteo-arthritis deformans, to ochronosis, to dysuria, etc. All these conditions are due to the infiltration of the tissues with the alkapton. Söderbergh found a positive Wassermann reaction in his alkaptonuric patients, which he ascribed to the homogentisic acid present in the blood.

Neuberg states that "no treatment for alkaptonuria is known, and, indeed, considering that the metabolic disturbance is harmless, and involves no danger to the patient, treatment is hardly necessary." Umber recommends dietetic therapy. He suggests a protein-poor diet, and especially the feeding of proteins poor in the homogentisic forming amino-aromatic compounds. A large fluid intake should be advised. For the joints, he suggests the usual therapeutic procedures of heat, heliotherapy, gymnastics, massage, and electrical treatment of the muscles adjoining the affected joints.

Cystinuria

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Of the sulphur in the protein molecule, our knowledge is not very extensive. Most writers have expended their energies on the cystin-sulphur fraction, and some have gone so far as to say that all the sulphur in protein is in the cystin combination. That comparatively little attention has been paid to this substance is shown by the fact that there elapsed three-quarters of a century between its discovery in a cystin calculus and its exact organic analysis.

In 1810 Wollaston(*b*), in a paper entitled "On Cystin Oxid, a New Species of Urinary Calculus," reported before the Royal Society of London the discovery of cystin, which he called cystic oxid, and which the Germans translated into Blasenoxyd, or bladder oxid.

Berzelius suggested that the name cystic oxid be changed to cystin. In 1838, Civiale wrote that, although this change corrected an error in chemistry, it perpetuated an error of physiology, for cystin is excreted by the kidneys and does not have its origin in the bladder (Garrod).

Cystin forms six-sided leaves or rhombic crystals. It is insoluble in water and alcohol. It is soluble in concentrated mineral acids. It is easily soluble in alkalies from which it can be precipitated only by organic acids, but not by mineral acids (Beilstein). In 1882 Mauthner called attention to the fact that cystin was levorotatory. Kulz(*b*), in a very short notice, in the same year stated that the levorotation of cystin was $-140°$. Mauthner made more careful determinations and found that in solution in hydrochloric acid (11.2%) ($\alpha D = -205.9°$.

Prout was the first to analyze cystin, but he overlooked the presence of sulphur. This analysis was confirmed by Pelouze. The credit for the discovery of sulphur in cystin is due to Boudrimont and Malaguti(*a*)(*b*), but they did not make a quantitative analysis. This was done by Thaulow in 1838. If we make a comparison of the figures obtained in the analysis of cystin by some of the older chemists we must observe how very close to the truth some of them were:

	Prout	Lassaigue	Thaulow	Marchaud	Gmelin
C	29.88	36.2	30.01	....	29.75
N	11.85	34.0	11.00	11.88	11.57
H	5.12	12.8	5.10	....	5.78
S	....	....	28.38	25.55	26.45
O	53.15	17.0	25.51	....	26.45

As Gmelin points out the figures of Lassaigue are so different from the rest that we must suspect that, through error, he analyzed a different substance.

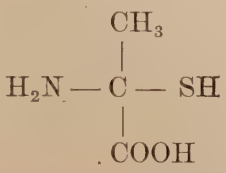
From his analytical data, Thaulow suggested $C_6N_2H_{12}O_4S_2$ as the formula for cystin. Gmelin thought, however, that the formula was $C_6NH_7S_2O_4$ and states: "According to this formula cystin is similar in composition to urethan and taurin." In 1864 Grote recommended the formula $C_3H_7NSO_2$ but Berzelius and Lehman adopted $C_6H_6NS_2O_4$ as the correct empirical formula.

In 1865 Cramer suggested C_2H_3 (S H) (N N_2) C O_2 H as the formula for cystin. But Dewar and Gamgee in 1870 took issue with this statement. They argued that if Cramer's formula were correct, oxidation of cystin would not yield glycerin but a sulfonic acid. They found that upon reducing cystin with tin and hydrochloric acid, hydrogen sulphid was evolved. From their experiments they suggested CH_2-$(NH_2)CS$—COOH as the graphic formula for cystin. This formula would suggest the possibility of cystin yielding methylamin by decomposition with alkalies, but Hoppe-Seyler found that he could not obtain methylamin and that the only nitrogenous body produced is ammonia, and he adopted the Gmelin formula, which he halved, i. e., $C_3NH_6O_2S$ and, although his hydrogen figures were rather low, he added one hydrogen to satisfy the Gmelin requirements, $C_3NH_7O_2S$. Kulz in 1884 discarded Gmelin's formula, and adopted the one of Thaulow. His hydrogen analyses were too high for the Gmelin formula, but agreed exactly with the formula of Thaulow.

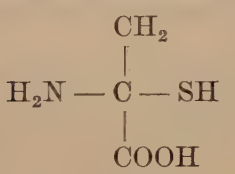
Baumann(*a*) corroborated the work of Kulz in an entirely different series of experiments. Upon reduction of cystin with tin and hydrochloric acid, he obtained a new substance which was a reduction product of cystin, and which upon analysis gave figures which approximated the Gmelin formula, $C_3H_7NSO_2$. He called this substance cystein, and he called attention to the similarity of cystein to a mercaptan which upon oxidation yields a disulphid:

$$\underset{\text{(Cystein)}}{2\,(C_3H_6NO_2SH)} + O = \begin{matrix} C_3H_6NO_2 - S \\ \\ C_3H_6NO_2 - S \\ \text{Cystin} \end{matrix} \Big/ + H_2O$$

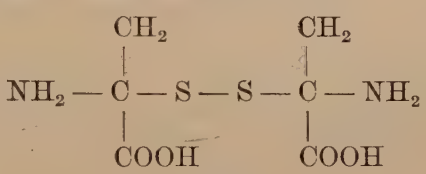
Baumann in collaboration with Preusse and Jaffe while working on the mercapturic acids proved rather conclusively that cystin was a disulphid. Even in their first researches with cystein, Baumann and Preusse suggested that the graphic formula of this substance was



if it could be demonstrated that upon action with alkali, H_2S, NH_3 and pyroracemic acid are formed. It had been shown by Dewar and Gamgee to their own satisfaction that pyroracemic acid could be formed from cystin by action of nitric acid. But this "finding" could not be corroborated by Brenzinger, who worked in Baumann's laboratory, and the formation of pyroracemic acid from cystin was shown to be an error on the part of the English chemists. Baumann thought that pyroracemic acid is an intermediary product in the decomposition of cystin. He, therefore, wrote the graphic formulæ of cystein and cystin thus:

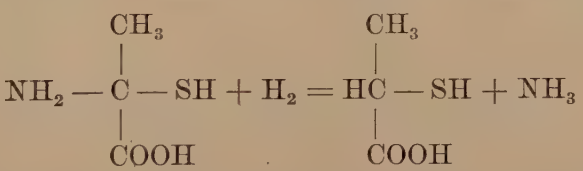


Cystein



Cystin

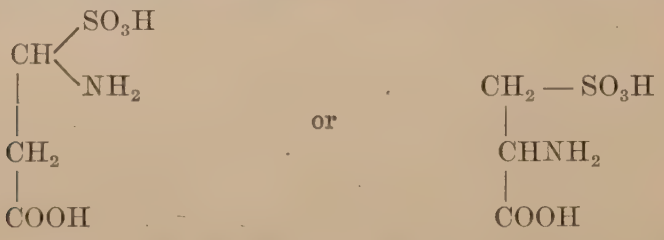
Corroborative evidence for this formula was added by Suter, who found among the cleavage products of horn substance α-thiolactic acid, which showed to be related as he thought to cystein, thus:



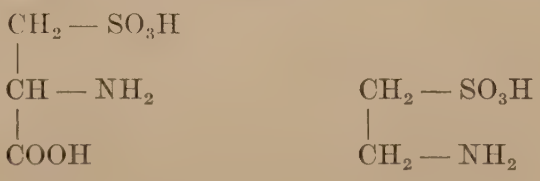
From the experiments of Suter, Baumann concluded that cystein is derived from α-thio-aspartic acid, and that it (cystein) is the mother substance of cystin, mercapturic acids and the thiolactic acid.

Friedman(*a*), in 1902, working with cystin applied Jochem's finding (that amino acids when treated with nitrous acid in hydrochloric acid solution were converted into corresponding chloro derivatives) to cystin and obtained dichlor-di-thio-propionic acid. Upon reduction, this substance gave β-thio-proprionic acid. From this Friedman concluded that

the sulphur atom was in the β position. He now investigated whether the amino group was in the α or β position. Upon oxidizing cystin with bromin, Friedman obtained cysteinic acid which would be either

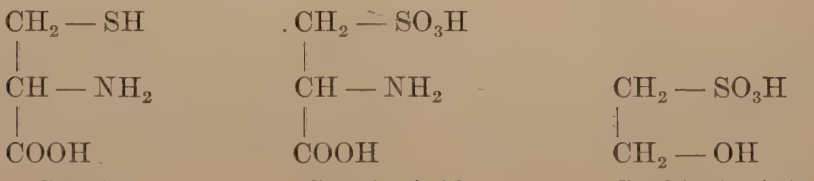


But upon heating this acid he obtained taurin, and this change could be explained only by the fact that cysteic acid has the formula:



Cysteic acid Taurin

In the same year (1902), Carl Neuberg also demonstrated that the sulphur and the nitrogen in cystein were attached to different carbon atoms. He treated cystin with nitric acid, which pointed to the correctness of Friedman's formula:



Cystein Cysteic Acid Isothionic Acid

From these reactions it is seen that cystin might be a precursor of taurin.

Cystin occurs in the protein molecule in union with the other amino acids. Quantitative analyses of the cystin fraction have yielded the following figures:

Globulin of hemoglobin (horse's blood)	0.3%
Egg albumin	0.3
Crystalline egg albumin	?
Serum albumin from horse's blood	2.5
Serum globulin from horse's blood	1.5
Fibrin	1.1

Bence-Jones' Protein	0.6%
Proto-albumose	0.7
Hetero-albumose (Witte's peptone)	4.1
Edestin (from hemp seed)	0.3
Crystalline globulin from squash seed	0.3
Protein from fir-tree seed	0.3
Gliadin from wheat	0.5
Caseinogen (cow's milk)	0.1
Caseinogen (cow's milk)	?
Koilin	0.8
Egg membrane from *Scyllium stellare*	?
Neurokeratin	1.5
Whalebone of North Whale	4.2
Carapace of tortoise	5.2
Keratin from ox horn	6.8
Keratin from sheep's horn	7.5
Keratin from sheep's wool	7.3
Keratin from horse's hair	8.0
Keratin from egg membrane	7.6
Crystalline protein from *Antiaris toxicaria*	10.6

Van Slyke determined the cystin nitrogen in various proteins and he gives the following figures expressed in percentages of total nitrogen:

Protein	*Cystin Nitrogen*
Gliadin (wheat)	1.25%
Edestin	1.49
Keratin (dog's hair)	6.60
Gelatin	0.00
Fibrin	0.99
Hemocyanin	0.80
Hemoglobin	0.00

Buchthala in his analysis of various substances rich in keratin obtained the following amounts cystin (expressed as per cent of total):

Human hair	A	14.03%
	B	12.98
	C	14.54
Human nails		5.15
Horse hair		7.98
Horse hoofs		3.20
Cow's hair		7.27
Cow's hoofs		5.37
Hog's bristles		7.22
Hog's hoofs		2.17

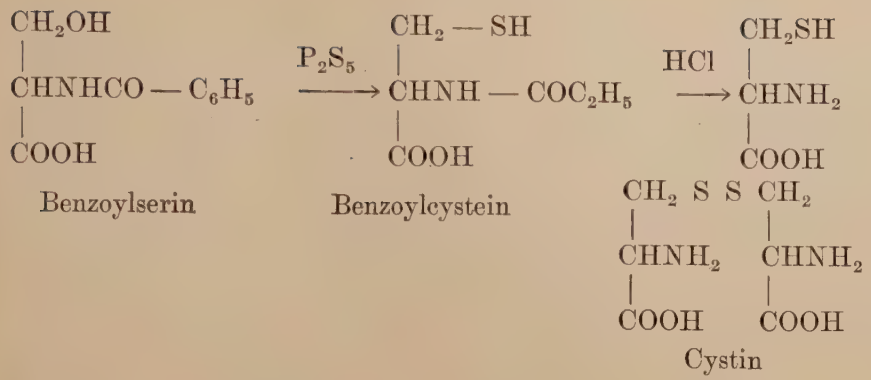
In the feathers of the goose, Buchthala found 6.3 per cent. He also analyzed the egg membranes of the *Scyllium stellare* and obtained 0.44 per cent cystin; of the *Pristiurus melanostomis* and obtained 0.60 per cent; of the *Scyllium canicula* and obtained 0.42 per cent. But attention is to be called to the fact that in the last three analyses Buchthala did not isolate the cystin, but determined the sulphur and computed the amount of cystin from the amount of sulphur present.

Cystin occurs rarely in human bladder concretions. It is more frequently present in the urine and calculi of dogs. In human urine it occurs in cases of cystinuria. Cloetta found cystin in cow's kidneys (1856). Scherer found it in the liver of a drunkard who died from typhoid fever, and Drechsel found it constantly together with the xanthin bases in the horse's liver. Magnus-Levy found H_2S upon autolysis of the liver which he states is derived from the sulphur of the cystin groups. In the protein of yeast, Schröder found 0.72 per cent sulphur. He boiled the protein for several hours with 12.0 per cent hydrochloric acid, and found that cystin was one of the products of hydrolysis. Arnold made extracts of liver, thymus, muscle, heart, brain, testicles, kidneys, intestines, lens and spleen, and he found that all the extracts that were protein-free contained cystin. He found most in the liver and spleen. Reis found cystin by the Arnold reaction only in normal eye lens; lenses which had undergone cataract formation did not give this reaction. Winterstein and Strickler found 0.05 per cent cystin in colostrum of milk. Drechsel found cystin in the liver. Baumann and Goldmann reported that cystin was present in normal urine, but Stadthagen(*a*) refuted this. Hofmann stated that cystin is present in the sweat of cystinuric patients.

In 1890, Kulz found that when he permitted 290 gm. fibrin, 270 gm. ox pancreas, 3 gm. salicylic acid and 1 liter water to stand at room temperature for fourteen hours, he could isolate cystin. That cystin is one of the products of peptic digestion of protein was demonstrated by Langstein, who isolated this sulphur compound, together with other amino acids after protein digestion.

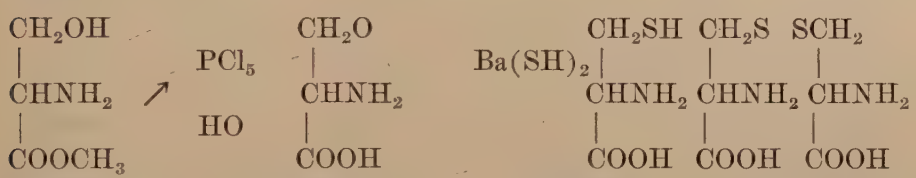
In 1869, Maly attempted the synthesis of cystin, but he was unsuccessful. He tried to condense a watery solution of aldehyd-ammonia, potassium sulphocyanate and hydrochloric acid. The resultant product was "cystin-like," but not cystin.

In 1903, Erlenmeyer, junior, reported the synthesis of cystin, and one year later in collaboration with Stoop, he gave a detailed description of his method. The stages in the synthesis are first benzoylserin which upon being heated with phosphorus pentasulphid produced benzoylcystein. Upon hydrolysis this yielded cystein, which upon oxidation lost hydrogen and changed to cystin:



Benzoylserin Benzoylcystein Cystin

Four years later Fischer and Raske synthesized cystin from the methyl ester of l-serin. From this they obtained by the action of phosphorous penta-chlorid and then by hydrolysis with hydrochloric acid l-α-amino-β-chloropropionic acid. By treating this with barium hydrosulphid, cystein was produced which when oxidized by a current of air yielded cystin:



Methyl ester of serin α-amino—β-chlor-propionic acid Cystein Cystin

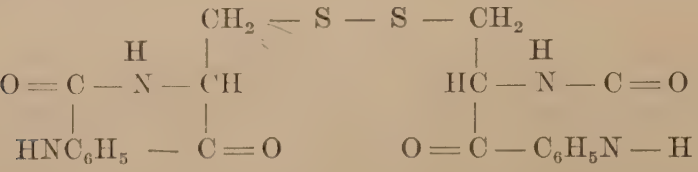
Of the identity of the cystin obtained from stones and cystin from protein decomposition, we need only mention the work of Fischer and Suzuki, who demonstrated the identity of hair cystin and stone cystin, and of Abderhalden, who compared protein cystin and stone cystin. Fischer and Suzuki found the rotation of hair cystin as —221.9° and of stone cystin —223.6°. Abderhalden found the following figures for the rotation of cystin:

Hair cystin α 20°	= —223.8°
Hemp edestin cystin	= —218.8°
Feather cystin	= —219.8°
Horn cystin	= —220.5°
Serum globulin cystin	= —221.2°
Serum albumin cystin	= —216.8°

That bacteria play an important rôle in the decomposition of cystin has been demonstrated in a number of instances. Herter, and later Goodridge, showed that upon growing the *Bacillus putrificus,* the *Bacillus*

lactis aërogenes, the *Bacillus coli communis* and the *Bacillus acidi lactici* in peptone solution containing cystin in suspension, the cystin was decomposed into either hydrogen sulphid or mercaptan.

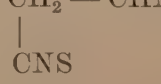
Before we take up the discussion of the metabolic derangement which results in the condition known as cystinuria or cystin calculi, we shall briefly indicate the methods for the detection and separation of cystin from urine. The microscope is a great aid in finding the typical cystin crystals. Patten suggested recognition of cystin by treating the urine with phenyl isocyanate and obtaining the crystals of cystin-phenyl hydantoin acid:



Arnold reported that copper cystin yields a reddish-brown precipitate with a 4 to 5 per cent solution of sodium nitroprussid, and a violet color with a sodium hydrate solution. Upon oxidizing cystin with potassium permanganate, Denis obtained oxalic acid, sulphuric acid, carbon dioxid, acetic acid, nitric acid, ammonia and sulphur.

The insolubility of cystin in water was called attention to by Wollaston and later Brücke laid much stress upon this fact, which, of course, is the explanation for the frequency of cystin calculi in the cystinuric individuals. On account of this insolubility, cystin does not yield a good Siegfried reaction. (Liebermann.)

According to Neuberg and Ascher cystin when treated with barium nitrate and sulphuric acid is desamidized into δ-oxy-β-thio-propionic acid. If the cystin is carefully distilled over a free flame the resulting compound is diamino-ethylen-disulphid. Mauthner obtained cystin as the copper salt from a patient suffering with cystinuria. By action upon it with zinc dust and lead oxid in ammoniacal solution he obtained alanin. By allowing potassium cyanid to act upon cystin for eight weeks, he obtained 1-α-amino-β-sulfocyanpropionic acid:



Delépine analyzed a sample of urine for Lauder Brunton for cystin, using Löbisch's method. He found that when a specimen was strongly acidified with acetic acid the precipitation took place more slowly than if the specimens were allowed to undergo a spontaneous acid fermentation.

When the fluid was carefully filtered the precipitation of cystin was delayed several days. Evaporation did not increase amount of cystin.

He concludes:

1. That the simple addition of an acid in which cystin is not soluble is not sufficient to separate cystin from the urine and that the theory held as to the state of combination of cystin in the urine is probably inaccurate.

2. That a compound exists in certain urines which under the influence of fermentation yields cystin.

3. That the fermentation is due to the growth of a large organism probably a torula.

4. Cystin occurs in kidneys and liver, showing fermentation may go on in the system.

Benziger, reporting his failure to synthesize cystin, wrote that with isocyanic acid cystin yielded a uramide acid which upon dehydration yielded hydantoins. Cystein is so seldom found in the urine because it oxidizes so easily to cystin. (Mathews and Walker.) From cystein, the benzyl derivative can be easily prepared by shaking benzoylchlorid with potassium hydroxid for one-half to one hour.

What the cause of cystinuria is has remained a puzzle to students of metabolism. That it is a derangement in catabolism is the general opinion, where the seat of derangement is not known. It is supposed that cystin is always produced in normal catabolism, but it is immediately broken down to other sulphur derivatives. Wohlgemuth stated that cystin was the antecedent of the sulphur bodies in the urine and of taurin in bile. When he allowed cystin to decompose with meat, he obtained a yield of hydrogen sulphid, methyl mercaptan, and ethyl sulphid, which are usual constituents of the intestinal gases.

Since Wollaston's case of cystinuria, many cases have been reported. In 1876, Niemann(*a*)(*b*) collected all the cases reported of cystinuria that he found in the literature. We shall cite him:

CASES

Author	*Sex*		*Age*
Wollaston	Boy		5 years
Wollaston	Man		36 years
Marcet	Man		30 years
Marcet	Man	Brothers	30 years
Marcet	Man	Brothers	30 to 49 years

[1] The identity of hair cystin and horn cystin was confirmed by Gaskell. In five cystin stones from St. Bartholomew's Hospital Museum the cystin was only found in the form of hexagons. Tyrosin was not present in them.

Author	*Sex*	*Age*
Brande	Man	.....
Brande	Man	40 years
Prout	Man	30 years
Stromeyer	Man	.....
Buchner	Man	.....
Magendie	Man	20 years
Yelloly	Boy	4 years
Venables	Woman	47 years
Neill	Woman	50 years
Bley	Man	.....
Willis	Man	.....
Prout	Boy	12 years
Segalas	Girl	15 years
Civiale	Man	25 years
Civiale	Man	23 years
Civiale	Man } Brothers	39 years
Civiale	Man } Brothers	37 years
Schwirg	Man	26 years
Lenoir	Boys, 2 Brothers	.....
Hodann and Miller	Boy	5½ years
Toel	Woman	.....
Toel	Woman } Sisters	28 years
Toel	Woman } Sisters	30 years
Schlossberger	.....	.....
Roberts	Woman	21 years
Heller	Woman	18 years
Heller	Man	43 years
d'Etrolles	Woman	.....
Bartels	Man	40 years
Bary	Man	23 years
Johnson	Man	.....
Marowsky	Man	44 years
Ivanchick	Man	49 years
Ultzmann	Man	24 years
Ultzmann	Boy	2 years
Ultzmann	Boy	7 years
Ultzmann	Man	35 years
Müller	Man	30 years
Ebstein	Man	18 years
Heath	Man	28 years
Harnier	2 Men	.....
Trendelenberg	Boy	2 yrs. 11 months (26 gm. stone)

The metabolic changes in cystinuria were studied by the earlier chemists in this field. Stromeyer and Prout reported that cystinuric individuals excreted daily less urea than normal individuals. Venables in 1830 described the case of a cystinuric patient who did not excrete any urea at all in the urine, a fact which appears very doubtful. Toel, in 1855, on the contrary found in his case of a woman who excreted daily 1.3 to 1.5 gm. of cystin, that the output of urea and uric acid was entirely normal. Löbisch, whose patient was a young physician, found that the excretion of cystin in the urine had no effect on the urea, uric acid and sodium chlorid output. Bartels(*a*) also did not find any change in the urea output in such patients. But Beneke confirmed Stromeyer and Prout's findings. He found less urea and uric acid in the urine of the cystinuric patient, and Sir Astley Cooper and Prout reported a case where no uric acid was found and the urea output was diminished. Willis found similar results.

Niemann and Cantani (1877) found the uric acid excretion diminished and the urea output normal. Simon observed a high uric acid content of the urine in his case and Stadthagen and also Leo(*a*) found a normal amount of uric acid in the cases they studied. Prechini and Conti, on the contrary, found the uric acid increased and the urea normal in the urine of their patient. These authors compare cystinuria to oxaluria.

On the other nitrogenous substances present in the urine together with cystin quite a number of researches have been made:

Von Udranszky and Baumann found in the urine of a patient suffering with cystin deposits in the bladder and cystinuria, certain basic nitrogenous substances—"ptomaines"—which they identified as cadaverin and putrescin. Neither the indol nor the phenol excretion was above normal. This would indicate that the intestinal putrefaction is not above normal. They also found diamins in the urine and feces of the cystinuric. Garcia examined this case four years later and found a higher diamin excretion than Udranszky and Baumann. Borissow also studied the same case one year after Garcia and obtained still higher figures. In two other cases studied by Brieger and Stadthagen similar results were obtained.

These diamins were found in the urine of such patients by Lewis and Simon, Simon, and other authors. The amount of these amino acids is not constant, having periods of increased and lessened excretion. (Garrod, Garrod and Cammidge, Schöllberg.)

Garrod(*g*), in his brilliant lectures on "Inborn Errors of Metabolism," gives a table showing the amount of cystin excreted by cystinuric patients. We cite his table herewith:

TABLE SHOWING DAILY EXCRETION OF CYSTIN IN 20 CASES OF CYSTINURIA

No.	Sex and Age in Years of Patient	Daily Output of Cystin, Calculated Average Unless Otherwise Stated	Method of Estimation Employed	Observers
1	M., 18	0.520 gm.	Precipitation by acetic acid	Niemann
2	M., adult	0.425 "	"	Loebisch
3	M., 25	0.241 "	"	Ebstein
4	F., 23	0.430 "	"	"
5	M., 13	0.186 "	"	Stadthagen
6	F., 41	0.1402 "	"	Leo
7	F., 29	0.19-0.3 "	"	Piccine e Conti
8	F., 65	0.464 "	"	Marriott and Wolf
9	M., adult	1.0 "	Mester's meth.	B. Mester
10	F., 50	0.423 "	"	Percival
11	F., adult	0.454 "	"	Moreigne
12	M., 28	0.469 " (calculated)	"	Caracciolo
13	M., adult	0.471 "	Concentration and acetic acid	Loewy and Neuberg
14	M., adult	0.561 "	"	Thiele
15	M., adult	0.4 "	"	Abderhalden and Schittenhelm
16	M., adult	On protein-rich diet, 1 grm.; On protein-free diet, 0.5 "	Alsberg and Folins method	Alsberg and Folin
17	F., 23	0.314 gm.	Gaskell's meth.	T. S. Hele, Case I
18	M., 63	0.412 "	"	T. S. Hele, Case II
19	M., adult	0.456 "	"	T. S. Hele, Case III
20	M., 44	Protein-rich diet, 1.31 gm.; Protein-free diet, 0.47 "	Alsberg and Folins method	Wolf and Shaffer

Hele found that the daily elimination of cystin was 0.3 to 0.5 gm. The amount of cystin in urine varied with the change in diet, but the variation is not proportional to the total sulphur or total nitrogen. In one case the administration of cystin per os was completely excreted as sulphate. Cadaverin was found only once in the urine.

That cystinuria is due to some defect in the intermediary metabolism of amino-acid is shown by the fact that van Amstel has described a case of alkaptonuria and cystinuria in the one patient.

Abderhalden and Schittenhelm found leucin and tyrosin in the urine of a cystinuric patient—a man, 34 years of age, who came from a healthy family. The patient was suffering from frequent attacks of cystic calculi. The urine was light yellow and quite clear. Upon standing the typical six-sided crystals of cystin separated. The reaction of the urine was acid, and occasionally it showed traces of protein. The daily urine excretion was 2000 to 2500 c.c. of a specific gravity of 1.012 to 1.015. Moreigne(*a*)(*b*) had also found these nitrogenous bodies in the cystinuric.

Bödtker(*a*)(*b*) reported three cases of cystinuria, one in 1892 and one in 1905, on one of whom he made extensive metabolic studies. He found no disturbance in nitrogen metabolism. The average daily output of neutral sulphur was 23.7 per cent of the total sulphur.

Abderhalden(*a*) reported the occurrence of five cases of cystinuria in children of the same family. One was a boy 21½ months old, the other a girl 9½ months old and the third a boy of 17 months old when they died. Two other children, boys, are alive but suffer from the same disturbance. In 500 c.c. of urine of the father, 34 years of age, Abderhalden found 0.046 gm. cystin. No cystin was present in the urine of the mother. In the urine of the paternal grandfather 0.07 gm. cystin was found in 500 c.c. of urine. In the urine of the paternal grandmother no cystin was found. Abderhalden calls attention to the fact that in the paternal side of the family there is a history of tuberculosis and gastro-intestinal disease.

Ackermann and Kutscher found lysin in the urine of a patient who excreted cystin. Ackermann, in 1913, reported that in addition to lysin, he found leucin and tyrosin in the urine. But the presence of amino and diamino acids in the urine is not constant in cystinuric patients. Wolff, Shaffer and Osterberg reported that they could not find any diamins in the urine. Hele found cadaverin once in the urine of his patient. It has been reported by Thiele that a meat diet increases the output of cadaverin.

Simon and Campbell did not find any amino acids, other than cystin, in the urine of their patient.

Abderhalden and Samuely fed cystin per os to a dog which increased the output of neutral and oxidized sulphur. With the progress of the experiment more and more of the cystin sulphur appeared in the urine in the oxidized state. Dialanyl cystin behaved similarly. When cystin, dialanyl cystin and dileucyl cystin were administered subcutaneously, the impression was obtained that the sulphur of the peptids is excreted less rapidly than the sulphur of the cystin itself.

The table on page 528 is a protocol of their results. They gave their animal 8 gm. dileucyl cystin subcutaneously, but they could not obtain any leucin in the urine. This shows that the dog burnt the entire amount of leucin given.

Calculating from the figures recorded for a number of cases of cystinuria, Garrod shows that the cystin : nitrogen ratio is variable. (See table on page 529.)

Wolf and Shaffer carried out extensive metabolic studies on patients excreting cystin.

Their results wholly confirm the findings of Alsberg and Folin, that sulphur of hair or protein-cystin fed to a cystinuric patient is normally oxidized to sulphuric acid, and are directly contradictory to the conclusion

Date	Diet 50 gm. starch 50 gm. meat 25 gm. fat	Oxidized S in 2 Days Urine gm.	Neutral S gm.	Total S gm.	Intake S gm.	Increase in S excreted gm.		Remarks
24-25, V.	.....	0.1327	0.0595	0.1922	.....	.....		
26-27, V.	.....	0.1803	0.0570	0.2372	.....	.....		
	1.0 Cystin							
28-29, V.	1.0 "	0.2958	0.3713	0.6671	0.5532	0.4646		
30-31, V.	.....	0.1540	0.1179	0.2719	.....	.....		
	Fresh meat							
1- 2, VI.	.....	0.1196	0.0921	0.2117	.....	.....		No cystin.
3- 4, VI.	1.0 Cystin	0.5090	0.1299	0.6389	0.5532	0.4427		No cystin.
	1.0 "							
5- 6, VI.	.....	0.1329	0.0943	0.2272	.....	.....		
	1.0 Cystin	0.5353	0.1852	0.7205	0.5532	0.5243		No thiosulphate.
7- 8, VI.	1.0 "							
9-10, VI.	.....	0.1292	0.1281	0.2573	.....	.....		
	Fresh meat							
11-12, VI.	1.0 Cystin	0.4718	0.1243	0.5961	0.5532	0.3831		
	1.0 "							
13-14, VI.	1.0 Cystin	0.6639	0.1607	0.8246	0.5532	0.6116	1.0358	Fore period lost. Benzoylchlorid test for cystin negative.
	1.0 "							
15-16, VI.	.....	0.2001	0.1520	0.3521	.....	0.1411		
17-18, VI.	1.6 1.6 Dialanylcystin	0.4710	0.1570	0.6280	0.5532	.....		
19-20, VI.	.....	0.2319	0.1933	0.4252	.....	.....		
21, VI.	Hunger	.....	.....	.....	.....	.....		
	Fresh meat							
22-23, VI.	.....	0.1584	0.0955	0.2539	.....	.....		
24-25, VI.	1.6 1.6 Dialanylcystin	0.4428	0.1182	0.5610	0.5532	0.4021		Urine no cystin.
26-27, VI.	.....	0.1668	0.1479	0.3147	.....	.....		
28-29, VI.	.....	0.1648	0.1133	0.2881	.....	.....		
	Fresh meat							
30- 1, VII.	.....	0.1503	0.0999	0.2502	.....	.....		
	1.6							
2- 3, VII.	1.6	0.4347	0.1928	0.6275	1.1064	0.9228		With β-naphthalinsulphochlorid no alanin.
4, VII.	1.6 Dialanylcystin	0.3852	0.0917	0.4769				
	1.6							
5- 8, VII.	.....	0.1665	0.1609	0.3274	.....	.....		
7- 8, VII.	.....	0.2125	0.2793	0.4917	.....	.....		

Name of Observers	Total N in 24 Hours Grams	C : N Ratio	Method of Estimating Cystin
Moreigne	4.13 16.8	7.4 : 100 4.8 : 100	Mester.
Percival	3.98 15.1	5.9 : 100 3.1 : 100	"
Alsberg and Folin	av. 5.19 av. 14.84	9.6 : 100 6.7 : 100	Absolute increase of neutral sulphur above normal average.
Abderhalden and Schittenhelm	12.0 16.6	3.3 : 100 1.08 : 100	Concentration and acetic acid.
Thiele	5.15 9.1 17.29	9.4 : 100 6.2 : 100 2.9 : 100	"
Hele, Case I.	4.30 11.16	5.2 : 100 4.2 : 100	Gaskell.
Hele, Case II.	6.52 16.90	5.52 : 100 3.37 : 100	"
Wolf and Shaffer	3.53 14.63	13.3 : 100 8.9 : 100	Absolute increase of neutral sulphur above normal average.

of Loewy and Neuberg, that cystinuric individuals are unable to oxidize ingested cystin.

Simon(*b*) also found that after feeding of tyrosin and leucin he could not obtain it in the urine; Gross and Garrod confirmed Simon's findings.

Several observers have noticed the occurrence of rheumatic diatheses in the cystinuric. Marowsky found cystin in the urine in a case of liver disease. In a case of syphilis Ebstein found cystin in the urine which he cured by treatment with mercury. Of course it must be borne in mind that Baumann and Preusse and Jaffe have caused artificial cystinuria by feeding the halogen benzols together with ethylcystin.

According to Wolf and his collaborators (Marriott, Williams, Shaffer), both cystein and cystin prepared from patient's urine were likewise oxidized when given by mouth. The cystin excreted in the urine is evidently not absorbed as such from the intestine, but must be absorbed in the form of a larger molecule; because cystin absorbed as such is oxidized.

They found that an increase of food protein leads to an increase of cystin excreted, but when the food protein is hydrolized outside the body and isolated cystin is given to a cystinuric patient, the sulphur of the cystin is oxidized to sulphuric acid.

Cystin injected subcutaneously was excreted in the form of neutral

sulphur (probably cystin). Cystein similarly injected led to an increase of total sulphur of the urine, the increase being equally divided between inorganic sulphates and neutral sulphur. The authors believe that cystin excreted by subjects of cystinuria has a double source. Perhaps the greater part is from the protein in the diet, that is, exogenous. The other part is endogenous and has no relation to the food.

One phase of the anomaly of cystinuria appears to consist in the inability to oxidize that part of the sulphur-containing protein which has not been split so far as the cystin stage in the intestine.

Rothera's experiments in this field are interesting: Cystin prepared by the hydrolysis of hair, as also a specimen of calculus cystin, when given by mouth to man, were completely oxidized to SO_4 and appeared quantitatively as such in the urine. Cholalic acid does not diminish the excretion of sulphate in the urine, as it might if cystin were a precursor of sulphate, and were converted to taurocholic acid. Cholalic acid given simultaneously with cystin does not interfere with its oxidation to sulphate. He conclusively established the identity of hair and calculus cystin. His attempts to get the liver to oxidize cystin to sulphate uniformly failed.

Magnus-Levy found hydrogen sulphid upon autolysis of liver. He thought that this hydrogen sulphid is derived from the cystein groups of the protein.

Thiele thought that in cystinuria there is present a defect in the sulphur removing ferments, or in the denitrifying ferments or in both.

Neuberg recognizes three different types of cystinurics:

(1) Mild type where there is a tolerance for tyrosin, cystin and asparaginic acid.

(2) Type in which cystin is excreted and there is present a diminished power to oxidize other amino acids on feeding these amino acids.

(3) Type in which cases the disturbance of the intermediate protein metabolism is so advanced that besides the excretion of cystin, other amino acids are spontaneously excreted, such as tyrosin, leucin, etc.

Arnold found that acid extracts of all organs, especially the liver, freed from protein by saturation with Na_2SO_4 at 34°-37° give the nitroprussid and NH_3 reaction. Liver extract gives also several other reactions characteristic of cystein; treated with a very little dilute $CuSO_4$ solution gives a fleeting violet color and then a gray precipitate; if this be dissolved by dilute H_2SO_4 and a drop of 4 per cent sodium nitroprussid be added, immediately a flocculent rusty brown precipitate is formed; with dilute NaOH the cystein copper compound gives a dark violet reaction, which persists for some time. The reactions for cystein disappear slowly when an extract is made alkaline, rapidly when it is treated with H_2O_2; pure cystein solutions show the same behavior. Cystein is a constant and essential constituent of animal cells.

Sasaki and Otsulka found that the following bacteria formed H_2S from cystein: coli, typhoid, paratyphoid, dysentery (Shiga-Kruse), dysentery (Flexner), mouse typhoid, chicken cholera, prodigiosus, Proteus vulgaris, anthrax, subtilis, cholera, vib. Metchnikoff, vib. Finkler-Prior, and Micr. tetragenus. The following yielded no H_2S: fluorescens, pyocyaneus, Staph. pyog. albus, Staph. pyog. aureus, and Staph. pyog. citreus. Mercaptan formation could not be detected. The staphylococci evolve H_2S from S and from proteins. All the bacteria evolve H_2S from S except fluorescens and pyocyaneus. No H_2S was formed from taurin or Na_2SO_4.

According to Saxl bactericidal action of various mucosa secretions of the body fluids is well known. The similar action of several unoxidized sulphur compounds suggested the possibility of cystin or cystein compounds acting in this way in the organism.

Feeding brombenzene to the dog leads to a conjugation with cystein to form bromophenyl mercapturic acid. This acid and its salts are about ten times as potent as phenol. Urine of the dogs fed with the brombenzene was found to be bactericidal and required no added preservative to remain sterile. On the other hand, the blood showed no such property nor did the addition of the acid to the blood render it sterile. Saxl concludes that this is not the type of compound which renders body fluids bactericidal.

Loewi and Neuberg found that cystinuric subjects failed to oxidize glycocoll well, 20 per cent appearing in the urine. Glycylglycin and tyrosin are completely oxidized by the patients and are not to be found in the urine after feeding them to the subjects. Williams and Wolff reported that adding protein to the diet of a cystinuric patient increased the output of cystin. Thiele found that starving the patient, changing the diet or feeding cystin to the patient did not in any way affect the daily excretion of cystin in the urine. Wolff and Shaffer, on the contrary, could influence the metabolism by dieting their patient. They found that with a nitrogen-poor diet, the rest-nitrogen was 16.4 per cent of the total nitrogen, whereas with a nitrogen-rich diet the rest-nitrogen was 12.4 per cent of the total nitrogen. The neutral sulphur in their case was 61 per cent of the total sulphur. When the patient was fed cystein or cystin the ethereal sulphates were increased in the urine, showing that the thio-amino-acids were oxidized. Hele also found that the daily output of cystin (as determined by Gaskell's method), which in his case amounted to 0.3 to 0.5 gm. daily, had no relation to the total nitrogen or total sulphur excretion. Upon feeding cystin it was oxidized and appeared in the urine as the sulphate.

Stolte injected the cystin into the circulation of animals and he found that it was excreted in the urine. He observed that the nitrogen

content of the urine was also increased. Gross reported that cystein is very soon changed to cystin.

Blum(*b*) fed cystin to dogs and rabbits and he found that there was a marked increase in the sulphate elimination in the urine. Subcutaneous injection of 1.1 gm. cystin did not cause any cystin excretion in the urine. The administration of cystin intravenously in the peripheral circulation produced a marked output of cystin in the urine in four hours. But upon injecting the cystin into the mesenteric vein, no cystin appeared in the urine, and there was no increase in the ethereal sulphate output:

Dog 1

Day	Urine Volume c. c.	Easily Split S in 50 c. c. gm.	Total S in 50 c. c. gm.	Total Amt. of Easily Split S gm.	Total am't of S gm.	Split S: S S = 100	
1	1025	0.00383	0.0615	0.07867	1.261	6.24%	
2	855	0.00391	0.0648	1.06679	1.108	6.03%	
3	750	0.01879	0.1422	0.2818	2.133	13.22%	Gave 9.6 gm. cystin per os in the morning Vomited at night.
4	260	0.00727	0.0422	0.03776	0.2092	18.05%	Very sick and died toward evening.

Dog 2

1	480	0.00213	0.03582	0.02046	0.3438	5.95%	
2	415	0.00294	0.0511	0.02413	0.4241	5.76%	
3	480	0.00450	0.1229	0.04317	1.181	3.67%	4.5 gm. cystin 10 o'clock in the morning.
4	335	0.00325	0.06274	0.02175	0.4243	5.179%	Urin—no albumin. Dog somewhat weak; otherwise normal.

Dog 3

Dog, wt. 9 K

Received 1.1 gm. Cystin in 90 c. c. 0.0075% Na_2CO_3 Solution Subcutaneously

Day	Urine Volume c. c.	Split S gm.	S gm.	Total Split S gm.	Total S	Split S: S	Remarks
1	355	0.01099	0.10965	0.07803	0.7783	10.02%	
2	290	0.01185	0.1546	0.06876	0.8759	7.85%	1.1 gm. cystin
3	275	0.01271	0.1446	0.06990	0.8065	8.67%	No albumin
4	375	0.00979	0.1447	0.07345	1.0850	6.77%	No albumin

Dog 4

Dog 9 K. 1.4 gm. Cystin in 50 c. c. 3% Na_2CO_3 into Jugular Vein

Day before...	300	0.00930	0.15895	0.05579	0.9536	5.85%	
2½ hrs. after..	290	0.02244	0.06547	0.1301	0.3798	34.26%	Injection of 1.4 gm. cystin
24 hrs. after..	355	0.00965	0.10905	0.06857	0.7749	8.84%	

Dog 5

Dog 13 K. 1.5 gm. Cystin in 70 c. c. 2½% Na_2CO_3 into Crural Vein

Day before...	?	0.01146	0.1699	?	?	5.97%	
4 hrs. after..	140	0.01160	0.1736	0.05638	0.4861	11.60%	Injection of 1.58 cystin
24 hrs. after..	230	0.00905	0.08714	0.03625	0.4008	8.84%	

Dog 6

Dog 30 K. 1.4 gm. Cystin in 40 c. c. 3% Na_2CO_3 in Mesenteric Vein

Day	Volume c. c.	Split S. gm.	S. gm.	Total Split S. gm.	Total S. gm.	Split S: S	Remarks
Day before...	530	0.008789	0.1207	0.09317	1.280	7.282%	
6½ hrs. after..	335	0.01153	0.09842	0.07722	0.6594	11.71 %	Injection of 1.4 gm. cystin
24 hrs. after..	410	0.006478	0.09514	0.05312	0.7793	6.816%	No albumin

Dog 7

Dog 31 K., Injected 1.4 gm. in Mesenteric Vein

Day before...	900	0.00505	0.06418	0.09086	1.107	8.21 %	
7 hrs. after..	300	0.00582	0.07455	0.03491	0.4493	7.78 %	Injected 1.4 gm. cystin
24 hrs. after..	600	0.00428	0.09147	0.05134	1.098	4.68 %	No albumin

Day	Split S 50 c. c. gm.	S. 50 c. c. gm.	Total Split S gm.	Total S gm.	Split S: gm.	Volume Urine c. c.	Remarks
8 days before cystin.	0.00946	0.06242	0.06624	0.4502	14.71%	350	Obtained on 3 days 0.01 gm. P subcutaneously.
Day before cystin.	0.00817	0.10465	0.09735	0.7598	12.81%	465	Somewhat jaundiced does not eat.
	0.00913	0.1225	0.12514	1.3720	7.46%	560	2.7 gm. cystin.
Day after cystin.	0.01011	0.0935	0.09097	0.8415	10.81%	450	
1	0.00667	0.09016	0.0604	0.8115	7.40%	450	6 days before 0.01 gm. P subcutaneously. Repeated 3 days before. Animal jaundiced.
2	0.00557	0.08742	0.02537	0.4021	6.31%	230	3.9 gm. cystin. 0.6 gm. of it vomited 6 hrs. later.
3	0.0077	0.08968	0.08473	0.7856	8.58%	550	

Pecchini's and Conti's patient was a woman, 29 years of age, who voided daily in her urine 0.19 to 0.25 gm. During the day hours she excreted 0.17 to 0.24 gm. and during the night hours 0.02 to 0.04 gm. of cystin.

Niemann found that the amount of sulphur excretion rises and sinks with the amount of cystin. The daily amount excreted by his patient was 1 gm. When the cystin was filtered off, the filtrate still showed a marked sulphur reaction, showing, according to him, the presence of soluble cystin. He calls attention to the fact that the presence of triple phosphate does not exclude the possibility of the presence of cystin.

The following figures were obtained by Mester for the sulphur partition in a cystinuric patient:

Total S in 50 c. c. Urine		Total SO_4 in 50 c. c. Urine		Unoxidized Total S
$AsBaSO_4$ gm.	AsS gm.	$BaSO_4$ gm.	S gm.	
0.264	0.03626	0.1425	0.01957	46.0%
0.288	0.03955	0.150	0.0206	47.9%
0.206	0.02829	0.120	0.0165	41.7%

Williams and Wolf conducted experiments upon a cystinuric patient, male, age 29 years, weighing 129 pounds. In the urinary examination cystin was determined upon a basis of the excess of neutral sulphur over

that present in normal urines. Diamins were looked for by the benzoylation method and by precipitation with phenylisocyanate. Increased protein ingestion was followed by increased cystin excretion. After cystin ingestion (by mouth) nearly all the sulphur was excreted as inorganic sulphate. Two grams of tyrosin given during one day was apparently destroyed. No diamins could be detected in the cystinuric's urine. Examination for leucin and tyrosin was also followed by negative results.

Wolf, Shaffer, Osterberg and Somogyi found that the anomalies of metabolism in cystinuria are low ammonia, high undetermined nitrogen and high neutral sulphur. High undetermined nitrogen in part is due to cystin, and in part to other amino acids. High neutral sulphur is probably due entirely to cystin. The cystin in the urine is largely, but not wholly, of exogenous origin. The cystin sulphur of the protein molecule is not absorbed as such. Cystin and cystein administered by mouth are catabolized to sulphate. When these are given subcutaneously they are partially oxidized and partially excreted unchanged. Undiminished tolerance for cystin given by mouth to the cystinuric was found confirming the results of Alsberg and Folin. Sulphur-free amino acids, administered by mouth, were quantitatively catabolized. Creatin and creatinin given the cystinuric by mouth were eliminated just as by normal individuals. Administration of sodium cholate did not noticeably affect the output of neutral sulphur. The administration of cystin by mouth appeared to raise the sulphur excretion in the bile. After diversion of the bile from the intestine by biliary fistula, the cystin disappeared from the urine, but results with other cases indicate that there is no causal connection here. High undetermined nitrogen continued after cessation of the cystin excretion.

The tables on page 534 are taken from the work of Wolf and his collaborators.

One quality of cystin stones is to be mentioned, i. e., their easy recognition by X-ray, as reported by Kienböck and Morris. Von Hoffmann observed that while in the bladder they are easily crushed and are incrustated with crystals of calcium phosphate, a fact which Wollaston suspected. Wollaston thus described the cystin calculus:

"In appearance these calculi resemble more nearly the triple phosphate of magnesia than any other calculus; but they are more compact than that compound is usually found to be: not consisting of distinct laminæ, but appearing as one mass confusedly crystallized throughout its substance. . . . These calculi have a yellowish semitransparency; and they have also a peculiar glistening luster, like that of a body having a high refractive density."

There is no doubt that cystin stones are more common than is thought on account of the fact that they do resemble the triple phosphate stones and for that reason are not investigated more thoroughly.

Volume	Sulphur as				Per Cent of Total Sulphur			100 Total S / Total N	100 Neutral S / Total N	Weight, kg.	
	Total gm.	Inorganic gm.	Ethereal gm.	Neutral gm.	Inorganic	Ethereal	Neutral				
540	0.336	0.127	0.030	0.180	37.8	8.6	53.6	8.3	4.5	.....	Low protein diet. 720 grams boiled rice, 120 c. c. cream about 200 gm. sugar.
1560	0.746	0.405	0.024	0.317	54.4	3.1	42.5	15.5	6.6		
415	0.420	0.222	0.041	0.157	52.9	9.7	37.4	13.8	5.1		
760	0.292	0.071	0.046	0.175	24.3	15.7	60.0	9.6	5.7		
700	0.353	0.098	0.034	0.220	27.8	9.9	62.3	10.6	6.6	.....	± 1 gm. cystein given hypodermically.
1040	0.327	0.069	0.042	0.216	21.1	12.9	66.0	8.9	5.8		
710	0.371	0.127	0.035	0.210	34.2	9.2	56.6	10.1	5.8		
900	0.381	0.092	0.043	0.246	24.1	11.3	64.6	10.5	6.8		
1020	0.341	0.066	0.039	0.244	19.3	9.0	71.7	10.0	7.1		
1070	0.376	0.108	0.034	0.234	28.7	9.0	62.3	10.8[1]	6.7[1]	.....	10 gm. asparagin (= 1.05 gm. N) given by mouth.
700	0.283	0.082	0.038	0.160	29.0	14.5	56.5	8.1	4.6		
1000	0.327	0.142	0.024	0.160	43.5	7.5	49.0	10.5	5.2	.....	5 gm. cystin (= 1.3 gm. S) given by mouth.
955	0.570	0.356	0.634	0.180	62.5	5.9	31.6	16.0	5.1		
930	0.320	0.096	0.026	0.200	30.0	7.5	62.5	9.5[2]	6.0[2]	.....	5 gm. creatin given by mouth.
800	0.295	0.084	0.042	0.170	28.4	13.9	57.7	9.3	5.4		
1450	0.747	0.342	0.033	0.370	45.8	4.7	49.5	18.4	9.1	.....	4 gm. cystein given hypodermically. T. 101° F. 3 to 5 p. m.
1320	0.353	0.082	0.024	0.250	23.2	5.8	71.0	12.5	8.9	50.3	Leukocytes, 20,000.
865	0.423	0.112	0.034	0.275	26.5	8.5	65.0	12.0[3]	7.9[3]	.....	5 gm. creatin by mouth.
500	0.300	0.071	0.022	0.204	23.6	8.4	68.0	10.0	6.8	.....	Leukocytes, 12,400.
590	0.332	0.089	0.034	0.210	26.8	10.0	63.2	9.2	5.8		
258	0.320	0.108	0.033	0.180	33.7	10.1	56.2	10.5	6.0	.....	3 gm. sodium cholate by mouth in 4 doses.
695	0.324	0.099	0.036	0.190	30.5	10.8	58.7	7.8	4.5		
1000	0.588	0.335	0.026	0.227	57.0	4.3	38.7	15.6	6.0	.....	1.72 gm. urine-cystin given by mouth.
1005	0.340	0.116	0.025	0.200	34.1	6.9	59.0	10.2	6.2		
980	0.292	0.067	0.034	0.190	22.9	12.1	65.0	9.2	6.0	.....	Leukocytes, 17,800.
980	0.265	0.073	0.027	0.165	27.5	10.2	62.3	8.0	5.0		
1460	0.326	0.094	0.032	0.200	28.8	9.8	61.4	8.6	5.3		
1810	0.572	0.176	0.042	0.354	30.8	7.4	61.8	7.1	4.4	52.0	Differential leukocyte count: lymphocytes, 40 per cent; polymorphonuclear, 59 per cent; transitional, 1 per cent.

[1] Calculated after subtraction of 1 gm. asparagin nitrogen from total nitrogen.
[2] Calculated after subtraction of 0.46 gm. creatin nitrogen from total nitrogen.
[3] Calculated after subtraction of 1.2 gm. excess creatinin nitrogen from total nitrogen.

Volume	Sulphur as				Per Cent of Total Sulphur			Cystin gm.	Cystin Sulphur gm.	Neutral S — Cystin S	
	Total gm.	Inorganic gm.	Ethereal gm.	Neutral gm.	Inorganic	Ethereal	Neutral				
930	0.744	0.391	0.067	0.286	52.6	9.0	38.4	0.433	0.115	0.171	
980	0.757	0.372	0.035	0.350	49.2	4.62	46.2	0.314	0.084	0.266	
1060	0.785	0.420	0.062	0.302	53.5	7.9	38.4	0.545	0.145	0.157	
1220	0.776	0.385	0.042	0.349	49.6	5.42	45.0	0.447	0.119	0.230	
1200	1.066	0.599	0.069	0.398	56.2	6.47	37.3	0.631	0.168	0.230	25 grams "Somatose" and 5 eggs added to diet.
1200	1.013	0.605	0.056	0.353	59.6	5.52	34.9	0.482	0.128	0.225	25 grams "Somatose" and 5 eggs added to diet.
1400	0.019	0.595	0.044	0.370	58.4	4.32	36.3	0.816	0.217	0.153	50 grams "Somatose" and 5 eggs added to diet.
1100	1.095	0.598	0.076	0.421	54.6	6.94	38.4	0.882	0.235	0.286	50 grams "Somatose" and 5 eggs added to diet.
1000	0.925	0.561	0.026	0.338	60.6	2.81	36.5	0.792	0.211	0.127	
870	0.873	0.534	0.018	0.321	61.2	2.06	36.8	0.780	0.208	0.113	
1070	0.837	0.491	0.002	0.344	58.6	0.239	41.2	0.433	0.115	0.229	
890	0.977	0.531	0.075	0.371	54.4	7.68	38.0	0.478	0.127	0.244	Ate turkey on preceding day.
840	0.868	0.464	0.116	0.288	53.4	13.36	33.2				
1210	1.683	1.240	0.008	0.435	73.5	0.475	25.8	1.567	0.418	0.017	5 grams cystin administered by mouth in three portions.
1050	0.913	0.522	0.059	0.332	57.2	6.47	36.4	0.645	0.172	0.160	
1160	0.843	0.422	0.050	0.371	50.1	5.93	44.0	0.540	0.227	0.227	
995	0.822	0.448	0.048	0.326	54.5	5.84	39.7	0.497	0.132	0.194	
1070	0.926	0.520	0.054	0.352	56.2	5.83	38.0	0.465	0.124	0.228	
1480	0.756	0.392	0.053	0.311	51.8	7.02	41.2	0.267	0.071	0.240	2 grams tyrosin administered by mouth in three portions.
1160	0.800	0.407	0.067	0.326	50.8	8.37	40.7	0.435	0.116	0.210	

Treatment of Cystinuria

The therapy of cystinuria deserves notice. No scientist has yet been able to influence the metabolism in such wise as to prevent excretion of cystin. Baer recommended the exclusion of protein from the diet and the ingestion of very much water in order to dilute the urine. Beale advised the use of ammonium carbonate which he thought will keep the cystin in solution. Simon found that on the addition of cholic acid, there was no reduction in the cystin output. Klemperer and Jacobi have recently advised alkaline treatment for cystinuria. On a test diet they found that the proportion of cystin in the urine became much reduced when the patient refrained from protein in the food. The amount also decreased remarkedly upon the administration of an alkali. Both the amount of sediment and the proportion of cystin present decreased to zero under the influence of from 6 to 10 gm. daily of sodium bicarbonate. This case shows that when the ordinary reaction of the blood does not permit the complete cleavage of the cystin, this can be accomplished by rendering the blood a little more alkaline.

According to Smillie cystinuria is best treated by a low protein diet, with the addition of sufficient alkali to keep the urine alkaline. Cystin crystals will practically disappear from the urine of a cystinuric when sufficient sodium bicarbonate is added to the diet to render the urine alkaline. The amount of sodium bicarbonate necessary to render the urine alkaline, when the patient is on a nitrogen intake of 10 gm. or more, is greater than can be well borne by the stomach. Sodium bicarbonate does not influence body metabolism in cystinuria, but simply renders the cystin soluble.

Neumann states that 170 cases of these conditions have now been reported. Of late years interest in cystin has notably increased. The author has seen two cases which he reports in great detail. The first case was a renal calculus. Family and personal history of the twenty-four-year-old girl was good. Up to a certain day her health had been perfect and the urine normal. Within two months the entire disease-picture developed. Upon admission she presented a high degree of pallor. Chest, abdomen, and general nutrition were without any finds. A tumor was palpable at the site of the right kidney with patient in left lateral decubitus. Left kidney seemed normal. Urine contained cystin crystals and blood corpuscles. A part of the diagnosis was therefore readily made. Under pyelography the X-ray revealed the presence of a stone in the kidney pelvis. Pyelotomy then revealed a cystin calculus. This was removed, everything healing cleanly. The patient, however, showed no corresponding improvement. The kidney which had shown numerous little points of suppuration at the operation continued to give trouble

and its fellow also began to show symptoms. The X-ray showed no calculi anywhere, nor did the urine contain anything abnormal save a few cystin crystals. An attempt was made to determine the amount of cystin secreted, but the maximum values found were not sufficient. It was easier to determine the number of crystals in the sediment of each portion of urine passed, in the hope of causing them to vanish. Treatment consisted of bed rest, milk diet, bicarbonate of soda. Cystinuria was greatly benefited, but there was a possibility that other kinds of stone would develop.

The Metabolism in Disease of Respiration and Circulation . . . . . *Francis W. Peabody and Edna H. Tompkins*

Interference with Gaseous Exchange—Effects of Lack of Oxygen—Incomplete Combustion of Protein, Carbohydrate and Fat—Acidosis—Studies of Basal Metabolism—Gaseous Content of Blood—Studies of Non-volatile Products of Metabolism in Blood and Urine—Metabolism of Inorganic Salts.

The Metabolism in Diseases of Respiration and Circulation

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The pathological alterations of the metabolism which occur in the diseases of the circulatory and respiratory systems are in general so similar that they may be conveniently taken up together. In the present consideration attention will be paid only to those changes which are the direct result of disturbances of the functions of the respiration or circulation. This, of course, does not include the processes other than functional occurring in pneumonia, pulmonary tuberculosis and analogous conditions, which are the result of infection or toxemia and which are considered separately under the appropriate heading. The early literature has been adequately reviewed by Matthes(*c*) in von Noorden's "Metabolism and Practical Medicine" (1907), and is only referred to here incidentally.

In relation to the metabolism of the organism, the respiration and the circulation perform the important functions of supplying oxygen to the tissues, removing the gaseous and non-volatile waste products of cellular activity, and transporting metabolites from one part of the body to another. As would be expected, therefore, disease of the circulation and respiration may affect the metabolism in a variety of ways. In the first place, there may be an interference with gaseous exchange, either between the air in the lungs and the blood (external respiration), or between the blood and the tissues (internal respiration), with a resulting lack of oxygen or accumulation of carbon dioxid. As will be seen, the latter, probably owing to the high rate of diffusion of carbon dioxid, is of comparatively little practical importance, while insufficient oxygen may produce most serious effects. Disturbances of gaseous exchange in the lungs, which may be due to such processes as bronchitis, pulmonary edema, and consolidation, can be studied by means of analysis of the gases in the blood and in the alveolar air. Disturbances of gaseous exchange in the internal respiration, on the other hand, such as might be due to circulatory failure, or indirectly to disturbances in the external respiration, are much

more difficult to determine and can be approached only indirectly through a study of the waste products of metabolism in the blood, urine and expired air. Interference with the circulatory function of the removal of the non-volatile products of metabolism can also be studied only indirectly, as there is no method of investigating their accumulation in the tissues in life. Some light on this subject may be gained by analyses of blood and urine. With regard to disturbances in the circulatory function of transporting metabolites from one organ to another within the body, there is no evidence of importance to be obtained.

In the diseases of the respiration and circulation, the pathological effects on the metabolism are so largely due to insufficient supply of oxygen that it may be well to review briefly the results to be expected from oxygen-lack. Studies upon normal men, under conditions of low oxygen pressure, will better represent what is to be expected in circulatory and respiratory diseases, than will a consideration of any other pathological condition in which the supply of oxygen to the body is abnormal.

In the expedition to Pikes Peak, Douglas and his collaborators carried out an investigation on the adaptability of the body to low oxygen tension. The rapid pulse rate and increased blood pressure upon first entrance into the low oxygen pressures seemed to be only emergency compensations. They lasted only until those body changes occurred which were permanent for the duration of the stay in the rarified atmosphere, and which might correspondingly be expected in circulatory and respiratory disorders. The percentage and total amount of hemoglobin, the erythrocyte count and the percentage saturation of the arterial blood with oxygen gradually increased. At the same time the total ventilation increased, and the alveolar carbon dioxid tension dropped, thus causing a higher alveolar oxygen tension than would otherwise have been possible. More recently, work in the Air Medical Service, United States Army, has largely corroborated these findings. If these compensatory factors fulfill their purpose and provide sufficient oxygen to the tissues for all ordinary demands of the body, there is only one change in the metabolism to be expected—an increase in the total heat production depending upon the excess energy of the organs taking part in the compensation. The cardiac and respiratory muscles are the most important. Plesch(*b*) valued the heat production of a heart with a rate of about 60 beats per minute as five per cent of the total metabolism of the body, and showed that its caloric output varied directly with its rate. He also estimated the heat production of the respiratory muscles as one-fourth more than that of the heart. Evans likewise showed, on isolated heart-lung preparations of dogs, that the metabolism of the heart varies closely with the rate of contraction. Therefore, the measure of increase in the metabolism is dependent upon the grade of the compensations, and it may fall upon one or all of the three

sources of body heat. In the Pikes Peak expedition, the metabolism at rest was only slightly above that found at sea level for the subjects under investigation. The respiratory quotient showed no change indicative of abnormal combustion. Bittorf reviewed the studies at high altitudes, and considered the increase generally found in the metabolism so large as to be caused by more than the muscular compensations and suggested physical influences such as cold and violet rays.

On the other hand, if the compensation cannot adequately meet the demand of the body for oxygen a considerable number of changes in the metabolism are theoretically possible. Practically very little work has been done where such a condition was present. Here again one would expect that the muscular compensatory efforts would raise the metabolism above the basal, but it has often been questioned, especially in treatises upon oxygen disturbances in anemia, as to whether the basal requirements are not actually lowered when the tissues continuously receive less than their normal supply of oxygen. The two influences may easily mask each other and leave a practically normal metabolism. Many writers suggest that oxygen-lack causes simply an incomplete combustion within the cells, rather than a lowering of the basal requirements.

The discussions in regard to incomplete combustion are founded upon few facts, but the possibilities are extensive and must be considered with regard to protein, carbohydrate, and fat. Either non-combustion or a breaking down into abnormal end-products may result. Bache and Auel, working on dogs under low oxygen pressure, repeated the findings reported by Araki(*c*) of non-combustion of carbohydrates, and consequent appearance of sugar in the urine under conditions of asphyxia. Various investigators (Boycott and Haldane, Ryffel(*a*)(*b*), Barcroft), on the other hand, have reported incomplete combustion of carbohydrate, as probably shown by the presence of a low alveolar carbon dioxid content, or of lactic acid in the blood or urine. From the lowered alveolar carbon dioxid, the report from the Pikes Peak expedition assumed this, together with the presence of other abnormal acid metabolites. The many treatises upon the conditions due to the lack of oxygen during strenuous bodily exercise show the presence of lactic acid.

The amount of protein burned has also been reported as decreased when there is oxygen-lack. Voit(*h*), however, states that most work upon the subject, as well as his own, shows an increase in the nitrogen output. Minkowski(*k*) reports the same. Lusk(*e*) states that after respiration of rarified air when lactic acid is eliminated in the urine, there is an associated increase in protein metabolism with an increase in the ammonia and amino acid output. Disturbances in the intermediary protein metabolism have been investigated only in the urinary products. Weiss considers the neutral sulphur as a measure of amino acid output. The chances for

incomplete breakdown of the many amino acids are manifold but largely uninvestigated.

Of the metabolism of fat in asphyxial conditions little is known except the general clinical fact that in certain diseases where the supply of oxygen is limited there is an increase in fatty tissue, "a fatty infiltration," as Lusk designates it, and the few reports of Ryffel as to the appearance of acetone bodies in some instances.

Most disturbances of the intermediary metabolism due to oxygen-lack, therefore, tend to produce acidosis. In fact, it is generally assumed, from the lowered carbon dioxid tension of the alveolar air and carbon dioxid combining power of the blood, in cases where normals are subjected to low oxygen pressure, that acidosis is present. Thus, as a last point of attack, the effect of acidosis itself upon the metabolism must be considered. Acidosis increases the total metabolism, as has been shown by Lusk and Benedict and Joslin. It increases the nitrogen output, and thus also the sulphur, with a large ammonia percentage (Lusk; Bostock; Stehle; von Limbeck; and Sawyer, Baumann and Stevens). It causes a larger output of creatin than normal (Sawyer et al.) and, from the work of Goto, Sawyer et al., and Stehle, it increases the mineral metabolism, especially of the calcium and phosphorus, and somewhat less of the sodium and potassium.

Under normal conditions, as has been indicated, there is a complete and harmonious interaction between the circulatory and respiratory systems, and their activity is largely regulated by the body metabolism. Both the respiration and the circulation are endowed with great reserve force which enables them to meet the requirements of the metabolism when it is raised many times above its resting or basal value. Thus, during severe exercise, the pulmonary respiration becomes deeper and quicker, so that the alveolar ventilation is increased. At the same time the heart beats more rapidly, delivers a larger output, and raises the circulation rate. As a result of this and associated vasomotor adjustments, the blood flow through the tissues is greatly augmented, an adequate supply of oxygen is provided and the waste products of metabolism are removed. This reserve power has a special significance in the diseases of the respiration and circulation, for it explains the fact that only when they are severely affected is there any interference with their normal function at rest. Pathological conditions affecting the respiration or circulation begin by causing a reduction of the normal reserve, so that the needs of the metabolism cannot be met if it is greatly increased. This is seen, for instance, in emphysema, or in early valvular heart disease, in which the metabolism at rest is carried on normally and without discomfort, but in which even moderate exercise may produce dyspnea indicating an imperfect gaseous exchange. It is only when the pathological process has advanced so that the reserve power of the circulation and respiration has been greatly

reduced, therefore, that one may expect any changes in the metabolism. This is found to be true clinically, for in patients with cardiac or respiratory disease in a "compensated" state, or without symptoms at rest, no changes in the metabolism have been observed.

Before taking up in detail the effects of disease of the circulation of respiration on the course of the various chemical changes in the body, it may be well to consider the oxidative processes as a whole, in their qualitative and quantitative relationships, as is shown by determinations of the oxygen consumption and carbon dioxid production. Fundamental abnormalities in the general method of heat production might furthermore manifest themselves in the respiratory quotient, which is found by the various methods used in determining basal metabolism. Several observations (Kraus(*c*), Grafe(*b*)) of extraordinarily low respiratory quotients in patients with heart disease suggested that there might be some qualitative abnormality of the metabolism in this condition, but later investigations have failed to confirm this, and make it probable that the low quotients were due to technical errors. Peabody, Meyer and DuBois studied the basal metabolism of patients with cardiac, or cardiorenal disease in the bed calorimeter of the Russell Sage Institute of Pathology at the Bellevue Hospital, New York. They found complete agreement in the results obtained by the direct and indirect methods of calorimetry, and the respiratory quotients were all within normal limits. This indicates that there is no profound alteration of the intermediary metabolism. The patients on whom these observations were made were, in part, cases with completely compensated cardiac lesions and, in part, cases with moderate insufficiency, as evidenced by slight difficulty with breathing even while at rest, but the series does not include any severely decompensated patients. There are obvious technical reasons which make it difficult, if not impossible, to determine the gaseous exchange of extremely sick patients with circulatory or respiratory diseases, but in the absence of actual observations on such subjects, no definite statement can be made with regard to the occurrence of qualitative changes in the metabolism in severe cases. The possibility of the existence in very sick patients, of an interference with the oxygen supply to the tissues, or with the removal of carbon dioxid, circumstances which would alter the respiratory quotient, must be borne in mind. This subject will be referred to again subsequently.

Quantitative studies of the basal metabolism or heat production were also made by Peabody, Meyers and DuBois. The results showed that in patients with compensated heart lesions the basal metabolism is within normal limits, but that in patients with dyspnea the metabolism may be increased 25 to 50 per cent above the average normal. This increase is not constant even in dyspneic patients, however, for it occurred in only nine out of the twelve subjects and was marked in only five. The cause of the increase of metabolism is not clear, but the evidence does not indicate

that it is due to acidosis. One factor may be the extra work of the respiratory muscles. Reach and Röder found that an increase in the minute-volume of air breathed is accompanied by an increase in metabolism, and also that an increase in the depth of breathing causes a rise in metabolism, even if the minute-volume remains constant. According to them an increase of minute-volume is brought about with less energy if the rate of breathing is increased than if the depth is increased. This observation has some bearing on the diseases of the respiration and circulation, for the dyspnea produced in these conditions is associated with a rise in the minute-volume of air breathed, and this rise is frequently dependent more on an increase of the rate than of the depth. Minkowski summarized his review on the metabolism in circulatory and respiratory diseases by the statement that most observations show either normal or slightly elevated metabolism, and he attributed the latter to muscular compensations. Reinhardt found increased carbon dioxid output in emphysema, and also explained it on the basis of the increased muscular effort of respiration. Hellin, working on rabbits with extirpation of one lung, Carpenter and Benedict(*a*) on a man with obliteration of the left lung, Veit on a man with the use of but one lung due to pleural exudate, all found no abnormality in the metabolism. Lundsgaard(*b*)(*c*)(*d*) states that the degree of unsaturation of the venous blood agrees with that of the oxygen absorption in compensated and uncompensated circulatory diseases. It is normal in the former and increased in the latter. Harrop(*c*) also found no abnormalities in the venous and arterial oxygen in cardiac cases without arhythmia, compensated and at rest, and remarked that the oxygen consumption was increased in decompensated cases and normal in compensated. Aub and Stern reported a case of heart block under thyroid therapy. Unfortunately no metabolism observation could be obtained before the institution of the therapy, but seventy days after its cessation the metabolism was normal.

While the gaseous exchange can only be determined in patients who are in moderately good clinical condition, investigations on the chemical changes in the body produced by diseases of the circulation and respiration can be carried out by other methods which throw direct or indirect light on the metabolism. As suggested above, the effect of disease on the external or pulmonary respiration, a function which is interfered with in both circulatory and respiratory disease, may be approached from the standpoint of the blood gases with a view to determine whether there is disturbance of oxygen absorption or carbon dioxid excretion. In this connection it is, of course, the arterial blood, in comparison with the venous, which is of particular interest, and only comparatively recently has a method been developed by which arterial blood can be safely and easily obtained in man. In 1912 Hürter published a considerable series of observations on the arterial blood gases. In compensated heart disease

he found the arterial oxygen and carbon dioxid to be normal, but in two out of three cases with decompensation (one with congenital heart disease) the oxygen content was slightly below normal. In none of his cases was there any evidence of retention of carbon dioxid. Harrop obtained similar normal results in analyses of the blood gases in compensated heart disease, and found the saturation of the blood abnormally low in seven out of nine decompensated patients. As compensation was regained and pulmonary symptoms disappeared, the oxygen content of the blood tended to rise. The average normal percentage saturation of the blood was 95.5, and in only three of the patients did it fall below 85, and the lowest saturation was 81.4. No striking variations from the normal were found in the carbon dioxid, although the decompensated cases frequently had amounts slightly below normal. In diseases of the lungs (tuberculosis, pleural effusion, pneumonia) Hürter found that the oxygen saturation was normal or slightly decreased and the carbon dioxid was normal. In a large series of observations on cases of pneumonia (lobar pneumonia, postinfluenzal bronchopneumonia), Stadie found that the arterial blood was rarely more than 90 per cent saturated with oxygen while his normal figures were between 85 and 98 per cent. A fall below 85 per cent was usually accompanied by the development of cyanosis, and no case recovered in whom the arterial saturation fell below 80 per cent. Six to twelve hours before death the arterial oxygen saturation was found as low as 32 per cent. These changes were apparently due to the mechanical effect of exudate and edema in the lungs, and not to the infectious process. The venous oxygen paralleled the arterial closely except in cases with failing circulation where it was disproportionately low. Lundsgaard found the oxygen unsaturation of the venous blood (difference between oxygen capacity and venous oxygen content) to be essentially normal in cardiac patients with compensated lesions, whereas it was much increased during periods of decompensation. Scott(*a*) has made observations on the total carbonate content of the arterial and venous plasma in patients with pulmonary emphysema, and finds it to be increased. Siebeck(*a*) likewise, from studies on the "reduced volume" or dead space and "effective middle capacity" or lung volume, concluded that the arterial blood in emphysema is oxygen poor, and carbon dioxid rich, in comparison to that of normal individuals.

As stated above, values for venous oxygen or carbon dioxid have less significance than those for arterial blood. This is likewise true of values for alveolar air. However, the carbon dioxid tension of the venous blood as shown by Van Slyke and Cullen, and of the alveolar air according to Peabody(*c*)(*f*), is of considerable significance in showing the presence of abnormal acid products which in respiratory and circulatory diseases with normal kidney function must be attributed to disturbed metabolism. On this basis, Porges, Leimdörfer and Markovici explained their findings of

low carbon dioxid tension of the blood in cardiac cases with dyspnea and the elevation of the tension upon improvement, as well as the normal tension in those cases without dyspnea. They explained the normal or elevated tension that they found in pulmonary cases on the basis of simultaneous occurrence of acid products due to incomplete combustion, and an accumulation of carbon dioxid due to the pulmonary involvement. In patients with heart disease, Peters made determinations of the carbon dioxid tension of both alveolar air and blood. The ratio between the two was normal in cases without dyspnea, but in those with dyspnea it was low. In individual patients it approached normal as the clinical condition improved, and fell again as they became worse. This low ratio is regarded as due to a retention of carbon dioxid, with the production of a carbon dioxid acidosis, which is a factor in the causation of dyspnea. In severely decompensated cardiac patients the plasma readings, which were slightly low, indicate an acidosis apart from that which would be implied by the observations on the alveolar air. Fitzgerald found low alveolar carbon dioxid in one case each of bronchitis, asthma, mitral stenosis, and congenital heart disease, while a normal tension was found in tuberculosis, pleurisy and emphysema, and a high tension in one case of mitral insufficiency with asthma and cyanosis, and in one of pulmonary stenosis. In Peabody's cases of decompensated heart disease, the alveolar carbon dioxid tension was usually normal or a little decreased, but the hydrogen-ion concentration of the blood, determined electrochemically, was normal. Beddard and Pembrey also found the carbon dioxid of the alveolar air reduced in decompensated cardiac patients. In none of these cases, however, were the evidences of acidosis, as judged by the alveolar air, of marked degree. On the other hand, Scott obtained a high blood and Hoover a high alveolar carbon dioxid in emphysema, while Friedman and Jackson found an elevated carbon dioxid content of the alveolar air in experiments upon dogs with mechanical obstruction to the expiration.

It is difficult to evaluate these results on the blood and alveolar air in their relation to the metabolism. It is clear that moderate circulatory or pulmonary lesions do not affect the oxygen content of the blood, but that with severe processes, usually associated with cyanosis, the oxygen content may be decreased. It is not at all certain that a moderate decrease in the oxygen content of the arterial blood will affect the metabolism in the tissues, but if the disease progresses actual asphyxia in all probability takes place and death results. Even if, however, the oxygen content of the arterial blood does not fall so low during life as to produce complete asphyxia of the tissues, it is quite possible that the moderate decrease, such as has been described in severe circulatory and pulmonary disease, may be sufficient to alter the metabolic processes in the tissues, without stopping them entirely. If this is so one may seek the evidence of it in alterations of the intermediary metabolism. The normal respiratory

quotients found in moderately sick patients do not indicate any changes in the intermediary metabolism, but it is again quite possible that they may occur in severely sick cases and evidences of them may be sought in a study of metabolic products in the blood and urine. The observations on carbon dioxid appear to indicate a moderate grade of acidosis in severely decompensated cardiac patients, and this is probably correctly considered as secondary to incomplete combustion due to oxygen lack. The carbon dioxid retention described by certain authors in pulmonary disease, and in some cases of acute cardiac decompensation may be a factor in producing dyspnea, but only through this would it have any important relation to the metabolism.

It has been suggested above that other indications of a disturbance of metabolism in the diseases of the circulation and respiration might also be derived from studies of the non-volatile products of metabolism in the blood and urine. It is unfortunate that few analyses of the blood in these conditions have been published, and that complete metabolism observations, with balance sheets of the intake and output, are almost lacking. Tileston and Comfort(*a*) determined the total non-protein nitrogen and the urea nitrogen of the blood in a large series of cases, and found normal values in compensated valvular heart disease, aortic aneurism, acute pericarditis with effusion, and acute endocarditis. In cases with cardiac insufficiency the figures were normal, or slightly elevated, except in one instance with marked failure of compensation in which the total non-protein nitrogen was 70 mg. per 100 c.c. of blood a few hours before death. The increase of blood nitrogen in severely decompensated patients is easily explained by the impairment of renal function owing to imperfect circulation. According to O'Hare(*b*), the urea nitrogen content of the blood in patients with vascular hypertension is normal unless there is an associated nephritis. Rowe(*a*) investigated the non-protein nitrogen, and also, by a refractometric method, the total protein, albumin, and globulin content of the serum in various diseases. In cardiac decompensation, with or without edema, there was a decrease of total protein, though not to the same extent as in chronic nephritis with edema. The percentage of globulin and non-protein nitrogen were slightly above normal, but in one case of bronchial asthma there was moderate elevation of the non-protein nitrogen with normal serum proteins. In conditions of venous stasis he found the total protein to increase, with a greater increment of albumin than globulin and no change in the non-protein elements.

Very little work has been done on the constituents of the urine in the diseases of the circulation and respiration, except in the case of pneumonia and tuberculosis, in which the elements of fever and toxemia enter. One might expect to find an increase in nitrogen excretion in association with dyspnea, especially since it has already been shown that there may be a considerable increase in basal metabolism. The earlier literature (see

Zugsmith and Kahn(*a*)) contains evidence of this, but the results are by no means constant. The most complete studies of the nitrogen balance in patients with heart disease and circulatory failure are those of Husche (1894). His observations include both the nitrogen intake and output, but owing to the difficulty of keeping sick patients on a diet which was sufficient to meet their caloric needs, as well as the great variation in the volume of urine from day to day, it is impossible to draw accurate conclusions with regard to the nitrogen metabolism. Even when, as frequently happened, the nitrogen excretion exceeded the intake, it was more plausible to explain this on the basis of insufficient diet, or a washing out of nitrogen by diuresis, than to consider it evidence of increased nitrogen metabolism. When the disturbance of compensation was of short duration Husche usually found little retention of nitrogen in spite of marked retention of fluid, but in other cases there was retention of nitrogen and a washing out when the volume of urine increased. Rise and fall in nitrogen elimination are in general associated with similar changes in the urine volume, but the two do not run exactly parallel, for accumulation and excretion of nitrogen is usually more rapid than is that of water. Husche found the percentage of urea and ammonia nitrogen in the urine were essentially normal, but in a number of cases the uric acid was both relatively and absolutely increased. He regards this as due to uric acid retention during periods of decompensation, and not as evidence of increased uric acid formation. Lindemann determined the excretion of endogenous uric acid in three cases of juvenile asthma, and states that it was at a low normal level. The elimination of uric acid administered to these patients was slow. Zugsmith and Kahn made very complete observations on the metabolism in two cases of asthma, and concluded that asthmatic individuals seem "to suffer from a condition of tissue suboxidation." The indications of this were an increased excretion of neutral sulphur and a low excretion of creatin. There was no evidence of an increased nitrogenous metabolism for both patients had a positive nitrogen balance. Stadtmüller and Rosenbloom, on the other hand, studied the neutral sulphur excretion as an index of endogenous nitrogen metabolism, and found it to be increased in a case of bronchial asthma, but normal in a case of chronic myocarditis with broken compensation. Ryffel examined the urine of five cases of heart disease, all of whom were in bed, and one with marked cyanosis, for lactic acid, but did not find it in amounts which were above normal. According to him, French, Pembrey and Ryffel found an apparent increase in two cases of congenital heart disease with cyanosis. Ryffel says: "It thus appears that in these cases the lactic acid of the blood rarely rises high enough to cause active excretion by the kidney. The acid of the blood during life has been found increased in heart disease by Zülzer, but it is in the cyanosis of acute pulmonary disease that the highest values of lactic acid should be expected,

as the tissues are usually well nourished to start with, and the metabolism is even higher than normal owing to the pyrexia." Strinsover found that the amount of formic acid in the urine did not exceed normal values in compensated heart disease, but that it was increased in conditions associated with asphyxia and in cardiac failure.

There are few facts available with regard to the metabolism of inorganic salts in the diseases of the circulation and respiration. The retention of sodium, calcium and chlorin in pneumonia is the result of the febrile condition and is not associated with the disturbance of the function of respiration. In the two cases of asthma studied by Zugsmith and Kahn there was a positive mineral balance. According to Magnus-Levy(*b*) there may be a retention of sodium chlorid in the tissues in certain cases of cardiac insufficiency, arteriosclerosis, bronchitis, and emphysema, without definite evidence of renal involvement. In general, however, in circulatory diseases the retention of inorganic salts either depends on renal insufficiency or is associated with water retention. Allen(*d*) found the blood plasma chlorids to be increased in cases of vascular hypertension without impairment of renal function, and he believes that this rise is intimately related to the rise in blood pressure. In a study of certain physical constants of the blood serum, Gettler and Oppenheimer found that in cardiac disease with edema the freezing point and ash content were normal, while the specific gravity, solids, and refraction were decreased. In arteriosclerosis no important abnormalities were discovered, while in cases with arterial hypertension the solids and freezing point were high. The problem of water retention in heart disease remains one about which little is known, because there is as yet no satisfactory method of studying the fluid lost from the body by way of the skin and lungs. Richter(*f*) states, however, that retention of water and retention of solids do not necessarily move parallel to one another.

The results derived from studies of the blood and urine on the metabolism of the diseases of the respiration and circulation are thus as incomplete and conflicting as are those on the gaseous metabolism. Deviations from the normal, when they are found, are slight. In cases of mild or moderate severity the various compensatory mechanisms are such that the metabolism is not affected. In cases with serious disturbances of the functions of the respiration and circulation the metabolism may be increased and there may be evidences of interference with oxidative processes. The latter probably occurs only in the more advanced cases, and the increases in metabolism when present would seem to be usually due largely to the muscular efforts which take part in the compensations, rather than to the production of asphyxia.

Pathological Metabolism of the Blood and Blood Forming Organs . . . . . *Samuel H. Hurwitz*

Introduction—Newer Aspects of Blood Destruction and Regeneration—Mechanism of Blood Destruction and Regeneration—Hemoglobin Pigment Metabolism—Metabolism in Diseases of the Blood—Basal Metabolism in Anemia and Leukemia—Protein Metabolism in Disease of the Blood—Purin Metabolism in Diseases of the Blood—The Partition of Other Nitrogenous Constituents of the Urine—Mineral Metabolism in Diseases of the Blood—Chemical Changes in the Nitrogenous Metabolites and Fats of the Blood—The Influence on Metabolism of Some Measures Used in the Treatment of Diseases of the Blood—Diet—Transfusion—Splenectomy—Röntgen-Rays and Radium—Benzol.

Pathological Metabolism of the Blood and Blood-Forming Organs

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Introduction

Our knowledge of the pathological metabolism of the blood and blood-forming organs is in a state of rapid change. New facts, gathered by new and improved methods, are constantly coming to light, and these necessitate revision of previous conceptions. Besides, the data at hand, although much increased of late, are by no means complete and the deductions arrived at by different workers are not in entire accord. This is particularly true of such subjects as the factors concerned in blood destruction and regeneration, protein metabolism in diseases of the blood and the effects upon the metabolic processes of such important therapeutic measures as diet, transfusion, splenectomy, the Röntgen rays and radium.

The following review of some of the main facts concerning these subjects is therefore presented with the realization that the findings upon which it is based may later become open to question, and that further observations may alter their significance. Certain of the results, however, are based on such carefully conducted experimental and clinical observations that it has seemed safe to make fairly definite deductions concerning them.

Newer Aspects of Blood Destruction and Regeneration

It is not possible in a limited space to summarize our present-day views concerning all of the important additions to our knowledge of blood destruction and regeneration. An endeavor has been made rather to take up those aspects of the subject in which sufficient work has been done to warrant some conclusions even though they be tentative. More particularly are the views concerning certain phases of the problem of blood destruction and regeneration undergoing considerable change. It was thought well, therefore, to preface the pages which bear more directly upon metabolism by a consideration of the problems relating to the

metabolism of hemoglobin and the blood-derived pigments, with a discussion of the regulatory influence of the spleen, liver, and bone-marrow and the effects of various diets on the decomposition and formation of hemoglobin. To these subjects much new and valuable knowledge has been added within recent years, and it is not unlikely that some of the results will have an important bearing upon the treatment of blood diseases in man.

Mechanism of Blood Destruction and Regeneration.—*The Destruction of Red Blood-Cells.*—It has long been recognized that in the healthy body there is a constant disintegration and regeneration of red blood-corpuscles. The exact rapidity with which this takes place and just where and how this destruction occurs are questions which still await solution. Estimates based mainly upon the daily excretion of the hemoglobin-derived pigments indicate that under normal conditions from one-tenth to one-fifteenth of all the corpuscles in the body are lost and replaced in twenty-four hours (Rous and Robertson(*a*)(*b*)). Judged by such calculations, the average life of the erythrocyte would be from ten to fifteen days. More recent work, however (Whipple and Hooper(*c*)), by proving that bile-pigments may have other sources than red blood-cells, has demonstrated a large possible source of error in such calculations. In fact, evidence gained by means of differential agglutination of red corpuscles *in vitro* would seem to show that the life cycle of the transfused corpuscle is at least thirty days (Hunter, W.(*a*); Ashby).

The literature on the normal methods of destruction of the red blood-cells is extensive, but inconclusive. As has been pointed out, two separate processes may be at work (Hunter, W. K. (*d*)). But more recent studies have established a third mode of red blood-corpuscle destruction.

The first mode of disposing of the erythrocytes is through the phagocytic activity of certain cells (erythrophages). Certain facts concerning this process have been well established. It is known that large endothelial cells in the spleen take up red blood-cells and destroy them and that blood-pigment is sometimes present in the Kupffer cells of the liver, indicating that they play a part in the destruction (Pearce and Austin). Under certain conditions, moreover, the lymph glands and the bone-marrow may perform a like function. That these erythrophages remove badly damaged or decrepit red corpuscles from the circulating blood under pathological conditions is evidenced by the increased amount of detritus which they contain after the action of substances which injure red blood-cells. Whether, in addition, these cells may play an active part in blood destruction by attacking and destroying relatively healthy cells is still open to question.

While some investigators hold that phagocytosis is of itself sufficient to account for blood destruction, Rous and Robertson(*a*)(*b*) as a result of their careful experimental studies, are inclined to the view that in man

fragmentation plays a more important part in normal blood destruction than does phagocytosis. They have found that normal blood regularly contains small numbers of fragmentation forms, microcytes and poikilocytes, and that accumulations of them are regularly present in the spleen, but are found only inconstantly in other organs.

That fragmentation also plays an important rôle in blood destruction under pathological conditions appears from their observations that microcytes and poikilocytes are observed in animals with severe anemia due to hemorrhage. These fragmentation forms, it would appear, are not put forth as such by the bone-marrow, according to our former conception, but are portions of young cells fragmented while circulating because being formed to meet the emergency they are in large part unable to withstand the wear and tear of function. They are fragmented, while still circulating, to a fine hemoglobin-containing dust. The cell fragments are rapidly removed from the blood. Their occurrence in large numbers in the spleen both of normal and anemic animals suggests that this organ exercises some important function in connection with these forms.

It is not probable that a hemolytic process, in the ordinary sense, plays an important part in normal blood destruction. Rous and Robertson in their search of the organs and circulating blood of their animals could find neither shadows of red blood-cells nor hemolyzing corpuscles anywhere. And, as is well known, free hemoglobin is almost never found in the normal circulating blood. Destruction of erythrocytes by hemolysis, however, certainly occurs in those pathological conditions where considerable quantities of free hemoglobin can be demonstrated in the blood-plasma and where hemoglobin passes into the urine.

The Regeneration of Red Blood-Cells.—Perhaps the most certain evidence of blood destruction is to be found in the constant activity of the bone-marrow in the production of new cells. Under normal conditions, the bone-marrow produces just a sufficient number of erythrocytes to replace those destroyed in the wear and tear of the body's existence, so that the total number of red blood-cells in the body varies but slightly. Any loss or destruction of erythrocytes calls forth a stimulation of the erythrogenetic function of the narrow proportional to the loss or destruction of blood, with a consequent tendency to return to the normal count. That the converse is also true follows from the experiments of Robertson (*c*) on plethoric animals. He was able to show that the supplying of fresh blood-cells by transfusion results, at least temporarily, in a lessening of marrow activity as determined by a fall in the percentage of reticulated blood-corpuscles. Bone-marrow activity, however, will compensate only so long and so far as it is functionally capable. When, for any reason, excessive loss of blood or increased blood destruction leads to exhaustion of the marrow, compensation fails and anemia results.

The *nature of the stimulus* to blood regeneration has been the subject

of much study. A thorough discussion of the present-day views concerning this problem is given by Morawitz(*c*). As he points out, the suggestion that a diminished oxygen supply to the bone-marrow may stimulate the new formation of erythrocytes gains support mainly from the finding of an abnormally large number of red blood-cells in conditions where there is a lessened oxygen supply to the body, either through the inspired air, as in high altitudes, or where there exists a difficulty in the absorption of oxygen through the lungs, as in congenital heart disease.

A critical examination of the evidence upon which this view is based makes it certain, however, that diminished oxygen supply is not the only stimulus which governs erythrogenesis. Oxygen deficiency, if present, usually results in the formation of acid bodies in the blood which give rise to a diminished carbon-dioxid tension in the alveolar air and a diminished carbon-dioxid combining power of the blood. One would expect such indirect evidence of oxygen lack to exist in acute and chronic anemias, where regeneration of blood-cells is going on actively. But the newer methods of study have failed to demonstrate with any certainty the presence in these conditions of a diminished carbon-dioxid tension in the alveolar air or a decrease in the carbon-dioxid combining power of the blood (Morawitz(*c*)).

It has been suggested by Itami(*a*)(*b*) and by Ritz that in addition to diminished oxygen supply, the products of erythrocytic disintegration may furnish a normal stimulus to the bone-marrow. Support for such an assumption comes from the active regeneration noted in anemias produced by hemolytic agents. Whether this stimulus is of the nature of a lipoid derived from the hemolyzed red blood-cell (Kepinow) or a complement-like substance contained in the serum (Carnot) is uncertain. Morawitz and others are more inclined to the former view.

Tests of Bone-Marrow Activity.—So long as the number of circulating erythrocytes remains constant, it may be assumed that a balance exists between blood destruction and blood formation. But if the count is rising or falling, it is difficult without special methods to estimate the relative rate and degree of blood destruction and regeneration. The value of urobilin estimations as a criterion of the rate of red cell disintegration will be discussed under hemoglobin metabolism. Some direct knowledge concerning the rate of blood formation has come from the application of vital staining to this problem. Besides a study by fixed blood-smears of the erythroblasts, Howell-Jolly bodies, Cabot ring forms and certain types of stippling as a means of estimating the effort required of the blood-forming organs to maintain the cellular elements at a certain optimum level, emphasis has been placed by recent workers (Pepper and Peet, Lee, Minot, Sappington) upon reticulated cells, platelets, and mitochondria as signs of bone-marrow stimulation.

By methods of vital staining (brilliant cresyl blue, pyronin-methyl-

green) a blue-staining reticulum is demonstrable in a very small percentage of normal red blood-cells; the normal figure for adults being one-half to two per cent. In pathological conditions calling for increased bone-marrow activity, reticulated cells have been found considerably increased. The percentage may vary from one to four per cent in anemias, and in cases of hemolytic jaundice they may reach the very high figure of fifteen to twenty per cent. Whether the reticula are nuclear fragments of immature erythrocytes or the results of a disease process is not yet definitely established. Their identification, however, is of the greatest diagnostic value, and their diminution or disappearance as the result of treatment may be taken as a sign of good prognostic significance.

A determination of the number of blood-platelets by the newer methods (Wright and Kinnicutt, Gram) also yields information of value concerning the activity of the marrow in blood formation. The value of platelet counts in this connection is based on the observation that their number is reduced in conditions with defective regeneration and that they may be increased after splenectomy in pernicious anemia (Lee). In diseased conditions a gradual change of these elements of the blood in the direction of normal figures may therefore be taken as a sign of improvement.

The estimation of the number of erythrocytes containing mitochondria may also prove to be a useful indication of the rate of red blood-cell formation (Sappington). Mitochondria are small bodies of a lipoid nature which occur in the cell protoplasm, and which may be stained in a specific manner. They are not demonstrable in the circulating erythrocytes of healthy adult mammals, but are regularly present in nucleated red blood-cells. Their occurrence in non-nucleated cells is therefore supposed to indicate that such erythrocytes are relatively immature.

The methods so far considered are for the most part qualitative. A more quantitative measure of the rate of blood regeneration may come from the recent work on the oxygen consumption of the formed elements of the blood, and more especially of the red blood-cells. It has been shown by Morawitz(*a*) and his co-workers that normal human blood consumed very little oxygen, whereas the oxygen absorption of the blood of patients suffering from the various types of anemia may be marked. Furthermore, it appears that this increased absorption is due to the young, unnucleated cells and not to the erythroblasts of the blood. Harrop(*b*) has recently confirmed these findings. He has also made the interesting observation that the oxygen consumption of the blood in various types of anemia is proportional to the percentage of reticulated cells present. The demonstration of increased oxygen absorption by present-day methods may therefore prove to be a more accurate quantitative index of functional variations in bone-marrow activity than microscopic evidence alone.

Hemoglobin Pigment Metabolism.—*The Breaking Down of Hemoglobin.—Regulatory Function of the Liver in Bile-Pigment Metabolism.*—Our conception of the decomposition of hemoglobin pigment and the cycle of the blood-derived pigments has been considerably changed by recent studies. The generally accepted view covering bile-pigment metabolism assumes that the liver has only an *eliminative* function in forming bile-pigments (Stadelmann(*b*), Minkowski(*c*)). This view briefly sketched is somewhat as follows: Degeneration of red blood-cells frees hemoglobin which is brought to the liver and there changed to bile-pigments which are excreted as waste products into the intestine. Here the bile-pigments are reduced to urobilin or stercobilin, some of which may be absorbed and returned to the liver and again thrown out in the bile or destroyed. Some of the urobilin may escape the liver and appear in the urine, especially when the liver is not functioning normally. Whipple and Hooper(*a*)(*b*) have brought forth seemingly incontrovertible evidence, however, to prove not only the existence of an extrahepatic formation of bile-pigments, but also that the liver has a *constructive* as well as the commonly accepted *eliminative* function in the formation of bile-pigments.

That the conversion of hemoglobin into bile-pigment may also occur outside of the liver has gained support from the fact that old extravasations of blood frequently contain pigments which are identical with bilirubin; but that the conversion of hemoglobin into bile-pigments may occur outside of the liver in sufficient quantity and with sufficient speed to give rise to icterus has been much discussed.

As a result of the experiments of Whipple and Hooper this question has been answered in a positive sense. Thus they have shown that hemoglobin introduced into the circulation of dogs, first with Eck fistula, second with Eck fistula and hepatic artery ligation, third with exclusion of the liver, spleen and intestine, and lastly, with head and thorax circulation, was changed to bile-pigments in much the same way and in about the same time (one to two hours) as in normal animals.

Some knowledge concerning the cells or tissues responsible for this rapid change of hemoglobin into bile-pigment has come from the further observation that bile-pigments were formed when hemoglobin was placed in the pleural and peritoneal cavities. This evidence points to the endothelium of the blood vessels as the active factor. So that it is not unlikely that this mechanism comes into play when the liver is excluded, or when there has been excessive destruction of erythrocytes with much hemoglobin freed in the plasma. Although under normal conditions it is quite probable that the liver acts merely as an excretory organ for the bile-pigments in the same way as the kidney does for urea, it is not inconceivable that, possessed of endothelial cells, the liver might itself produce some of the pigments not only from hemoglobin freed from dis-

integrated erythrocytes, but also from substances added to the diet. In fact, the available experimental evidence suggests that bile-pigment formation normally may depend upon the functional activity of the liver cell, and that pigments may be formed, in part at least, from other substances than hemoglobin. It has been noted, for instance, that whereas the excretion of pigment from a biliary fistula is remarkably constant in a dog fed on a mixed diet, the output increases, sometimes by 100 per cent, when the diet is changed to one of carbohydrate, and is depressed on a diet of meat. Such evidence certainly strengthens the conception that bile-pigments may be elaborated by the liver cell *de novo* out of materials other than broken down hemoglobin, and that this constructive ability of the liver in pigment formation can be modified by diet.

The Building Up of Hemoglobin.—Liver Cell Activity and Diet Factors.—The constructive phase of the life cycle of hemoglobin pigment is not well understood. A working hypothesis, which is in accord with certain of the facts of pigment metabolism, has been proposed by Addis. According to this view hemoglobin is constantly liberated in the body from the disintegration of worn-out red blood-cells. The hemoglobin thus set free passes into the blood-plasma and is taken up by the Kupffer cells, which pass it on to the liver cells. Here the pigment is separated from the globin, and after the removal of iron and undergoing intramolecular changes which involve the addition of oxygen is converted into bilirubin. The bilirubin is reduced to urobilinogen in the intestine, a part escaping in the feces, and an important part being absorbed into the blood, polymerized into *urobilin-complex,* and taken up by the liver. In the liver this complex has restored to its pyrrol nuclei the original side chains, and then is used to form new hemoglobin molecules, or, if the liver is abnormal, may escape into the blood and appear in the urine as urobilinogen.

This theory has been subjected to critical analysis by Whipple and Hooper. And although it is as yet difficult to draw definite conclusions from their findings, considerable doubt has been thrown by their well-planned experiments upon the correctness of the older view that a considerable fraction of the bile-pigments eliminated into the intestine from the liver is reabsorbed and reutilized. Their work gives experimental evidence against the conception of a circulation of bile-pigments and presents proof of the existence of the same relationship on the part of the liver to the constructive mechanism of hemoglobin regeneration and its modification by diet as has been shown to exist for bile-pigment production. That the liver can form hemoglobin out of various materials other than the degradation products of hemoglobin follows from the observation that blood-pigment regeneration proceeds at a normal rate in a

bile fistula dog with bile-pigment excluded from the intestine (Hooper(*a*)). Under such circumstances the absorption of any pigment substances (bile-pigment, urobilin or urobilinogen) from the intestine is out of the question. It does appear, however, that under certain conditions as in acute regeneration following anemia, the body may conserve the substances which are suitable for the elaboration of hemoglobin (pyrrol nucleus). Evidently the pyrrol complex is a peculiar feature of the hemoglobin molecule, which the body carefully conserves for the purpose of reconstructing the hemoglobin molecule.

Whether the building stones which go to make up the hemoglobin molecule may arise also from certain elements of protein catabolism is not known. From the available experimental evidence, it would appear that both the products of protein catabolism as well as certain factors in the diet contribute to the steady construction of hemoglobin pigment.

The demonstration that the curve of hemoglobin regeneration can be influenced by various diet factors (Whipple and Hooper(*a*)(*b*), and Hooper, Robscheit and Whipple(*a*)(*b*)(*c*)) is very interesting and of the greatest significance in the treatment of anemia in man. It has been shown, for instance, that meat protein (beef, beef heart) and liver give a maximum hemoglobin production, whereas certain carbohydrates (bread, milk, crackermeal, rice, potato) or some of their ingredients, such as casein and gliadin give a minimum curve of pigment regeneration. On the other hand, gelatin or its mono-amino acid fraction, and hemoglobin itself administered either by mouth, intravenously, or intraperitoneally exert a distinctly favorable influence upon blood regeneration. Contrary to expectation, it has been found further that sugar feeding is less favorable for hemoglobin regeneration than is starvation. It is believed by Whipple and his co-workers that this observation may be explained by the protein-sparing action of sugar. Under conditions of starvation, the body may conserve certain substances resulting from the breaking down of body protein and use them over again in the construction of hemoglobin.

These studies on the relation of liver cell activity to the metabolism of blood-pigments indicate that the liver has a more important blood-building function in adult life than has hitherto been ascribed to it. Upon its functional activity depends not only the level of bile-pigment and hemoglobin production in the body, but there is much experimental evidence that its functional integrity is concerned with the maintenance of a normal level of plasma (Whipple, Meek(*a*)(*b*)) and serum proteins (Kerr(*a*)(*b*)(*c*)). In these instances, also, has evidence been produced that this particular activity of the liver may be modified by the materials brought to it not only from the products of tissue catabolism but also from certain substances in the diet.

Methods for the Determination of the Rate of Hemoglobin Destruction.—In the paragraphs on tests of bone-marrow activity, it was pointed out that the red blood-cell count depends, for the most part, upon the relative rate of blood formation and blood destruction. Even when blood formation is going on rapidly, the total count may be low because of rapid destruction of red cells, or the count may rise rapidly without any stimulation of the blood-forming organs due to diminished red cell destruction. It is therefore desirable to obtain more exact knowledge concerning the degree and rate of erythrogenesis and hemolysis by more reliable criteria. This is of particular importance in such diseases as pernicious anemia and hemolytic icterus where it is of value to determine the effect of such therapeutic measures as splenectomy and transfusion upon the rate of blood destruction and regeneration.

Whereas the methods for the study of the rate of blood regeneration are largely qualitative, there are fairly accurate indirect ways of estimating the extent of blood destruction. Of these, two methods only merit consideration: first, the estimation of the amount of urobilin excreted in the urine and feces; and second, the determination of the tolerance to injections of hemoglobin.

The generally accepted view of the origin of urobilin is based upon the assumption of a circulation of bile-pigments. According to this conception, the bile-pigments are changed to urobilin by the reducing bacteria in the intestine. The urobilin thus formed is in part excreted in the stools, in part destroyed, and in part resorbed by the portal blood stream and returned to the liver. Should excessive hemolysis occur there will be an increased excretion of bile-pigments by the liver and a corresponding increase in the amount of urobilin formed in the intestine. Much of this excessive urobilin leaves the body in the stools, but inasmuch as a large amount is also absorbed by the portal capillaries, an unusual strain is thrown upon the hepatic mechanism which serves to remove this from the blood. Not infrequently, therefore, considerable urobilin escapes into the general circulation and is excreted by the kidneys. Urobilinuria may then occur in conditions of increased hemolysis; but it may be found also in conditions unassociated with evidences of hemoglobin disintegration. In such instances, it must be assumed, urobilinuria results from an overflow through a poorly functioning liver in which there is interference with the normal function of removing urobilin from the blood. It is because urobilinuria may occur in conditions other than those associated with excessive blood destruction, that emphasis has been placed on the examination of the stool as well as the urine.

Although an unusual degree of blood destruction results in a greatly augmented quantity of urobilin in the stool, there is no absolute quantitative relationship between the actual amount of urobilin formed and the amount of blood destroyed. There are two reasons for this: first, the pro-

portion of urobilin absorbed from the intestine may be variable, some being destroyed and some resorbed by the portal blood, although unquestionable proof of this is lacking (Hooper(*c*)); second, there is evidence that some urobilin may be produced at times in the liver, and that liver function may in part govern its formation (Whipple(*b*)). It is therefore important in a discussion of the influence of blood destruction on urobilin excretion to bear in mind the probable hepatic origin of urobilin.

In spite of these sources of error, however, estimations of the amount of urobilin in the urine and feces give a fairly accurate index of the degree of hemoglobin destruction; especially if the quantity of urobilin in the feces be compared in any instance with the normal. The figures so obtained are of sufficient accuracy for clinical purposes.

Another method which promises to give information of value in regard to the rate of blood destruction has been described by Sellards and Minot. They have found that it is possible to inject, without danger, concentrated sterile solutions of hemoglobin into patients for the study of blood destruction; and that such injections will cause hemoglobinuria in patients showing evidences of increased blood destruction more frequently than in normal controls. To a certain extent, this method yields results of quantitative value inasmuch as the amount of hemoglobin needed to induce hemoglobinuria is directly proportional to the degree of blood destruction. And it is further of interest that the tolerance to hemoglobin can be shown to be low in conditions which are usually associated with increased elimination of urobilin. The underlying basis of the two methods of study is, however, quite different. Whereas, the urobilin output depends, in part at least, upon the amount of blood-derived pigment excreted from the body, hemoglobin tolerance depends upon the amount of pigment which accumulates in the body.

The Regulatory Influence of the Spleen in Blood Formation and Destruction.—The problem of the relation of the spleen to blood formation and destruction has been the subject of numerous studies on patients and on animals. A large amount of contradictory evidence has been gathered which it is difficult to correlate. With regard to certain of the experimental observations, however, there appears to be some uniformity of opinion.

Nearly all investigators attribute to the spleen a function in the destruction of red cells; and some ascribe to it a part in red cell formation; while some are inclined to the view that the spleen is concerned both with the regeneration and the destruction of blood. An effort will be made to analyze briefly the evidence for these opposing views.

The conception that splenic function is essential for red cell formation is based largely on the fact that in fetal life erythrocytes are formed in the spleen, and that under pathological conditions myeloid metaplasia may occur in this organ. That this erythrogenetic function may in some

indirect way be regulated by the spleen under normal conditions even beyond fetal life is not at all improbable.

It is known, for instance, that splenectomy in animals may often be followed by an anemia, which reaches its height in from three to six weeks, after which the blood gradually returns to the normal (Musser, Jr., and Krumbhaar). It has not been determined, however, with any certainty whether the anemia which follows the removal of the normal spleen is due to increased blood destruction or to diminished blood formation. Some rough index as to the preponderance of one or the other of these two processes has been sought for in determinations of the bile-pigment excretion in splenectomized animals. While it is maintained by Martinotti and Barbacci and by Pugliese that after splenectomy the output of bile-pigments drops to one-half normal, suggesting that excision of the

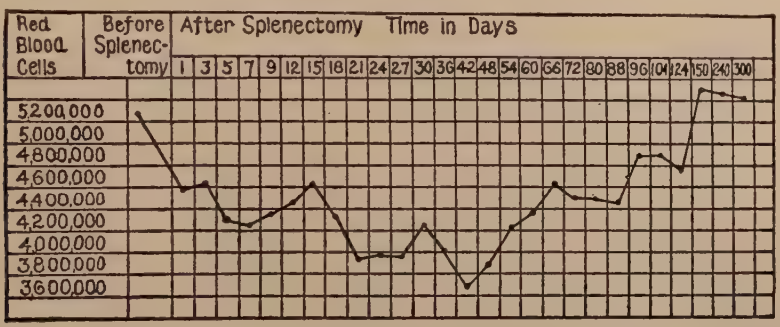

Fig. 1. Composite curve of the red blood-cell count of seven dogs after splenectomy. (After Pearce, Krumbhaar and Frazier, "The Spleen and Anemia," J. B. Lippincott Company, 1918.)

spleen in normal animals diminishes blood destruction, this observation has not been confirmed by the careful experiments of Hooper and Whipple(*d*). These workers found that a bile fistula dog will put out the same average amount of bile-pigments whether *with* or *without* a spleen. According to this it would appear more likely that the anemia results from a diminished activity of the blood-forming organs, notably the bone-marrow.

The evidence for this assumption, although not absolutely conclusive, is very suggestive. For instance, it has been found both by Pearce and his co-workers (Krumbhaar and Musser, Jr.) and recently confirmed by Hooper and Whipple(*d*) that the repair of an anemia produced by hemolytic poisons or by bleeding usually runs a longer course and is accompanied by less rapid regeneration of the blood in a splenectomized than in a normal dog. It may be, therefore, that the absence of the spleen is responsible in some way for the slow blood regeneration.

A possible explanation of this retardation of repair in splenectomized animals, and additional evidence in support of the view that the *normal* spleen may exert a stimulating effect on the bone-marrow has come from a

study of the influence of splenic extract upon blood formation. Danilewsky and Krumbhaar and Musser found a surprising increase in hemoglobin and red blood-corpuscles in the peripheral circulation after a single subcutaneous or intraperitoneal injection of extract of spleen. In view of the tendency to anemia following splenectomy, this work would suggest that the spleen may exert a stimulating effect upon the formation of red blood-cells in the marrow, were it not for the fact that the evidence for such a conclusion is contradictory and incomplete. Thus, Downs and Eddy very recently found that the subcutaneous injection of protein-free splenic extract is followed immediately by a *decrease* in the number of erythrocytes in the circulating blood, which they attribute to a direct hemolytic action of the splenic agent. And Krumbhaar and Musser could not establish that the feeding of fresh spleen to splenectomized animals influenced

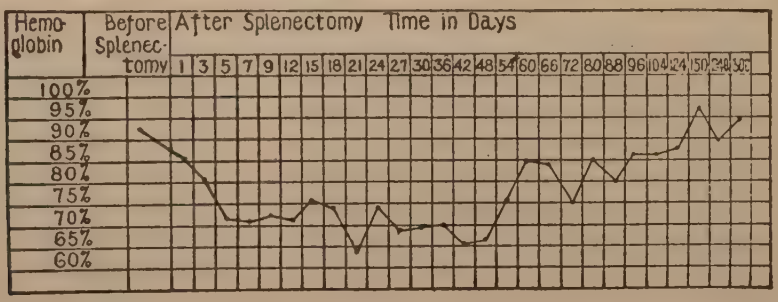

Fig. 2. Composite curve of the hemoglobin estimation of seven dogs after splenectomy. (After Pearce, Krumbhaar, and Frazier, "The Spleen and Anemia," J. B. Lippincott Company, 1918.)

in any way the anemia which usually follows splenectomy; nor do the careful histological studies of the bone-marrow made by Pearce and Pepper support this view. While the bone-marrow was not markedly changed during the first two or three months after splenectomy, there was ultimately an increase in the red marrow at a time when the anemia had improved. This late transformation of a fatty into a red marrow they regard not as compensatory to the early anemia caused by splenectomy but rather as a taking over by the bone-marrow, in the absence of the spleen, of the function of storing and elaborating the iron of the old blood-pigment.

Although there is some support for the theory that the spleen may play a part in blood formation, the tendency in recent literature has been rather to emphasize its function in the destruction of red blood-cells. The experimental and clinical evidence for such a conception of splenic function is attractive but not conclusive. Its main experimental basis is the observation that splenectomy in animals results in an increased resistance of the erythrocytes to various lytic agents and to the mechanical effects of shaking, and that such hemolytic agents as hemolytic serum, saponin,

and cobra venom, following the removal of the spleen, show a lessened tendency to cause hemoglobinuria and jaundice (Bottazzi, Banti(*a*), Pugliese and Luzzatti, Dominici, Joannovics, Karsner, Pearce, Austin and Krumbhaar, Gates). As a result of these findings the theory was advanced that the spleen was concerned in some way in influencing the normal destruction of worn-out erythrocytes, and that, as this influence was lost after splenectomy, hemolytic agents were correspondingly less effective. Botazzi, who was the first to demonstrate that the red cells after splenectomy showed an increased resistance to hemolysis in hypotonic salt solutions, used this observation as the basis for his hemocatatonistic conception of splenic function. This view has received support from Banti (*b*)(*d*)(*c*) and Furno, who regard the spleen as an organ concerned in hemolysis.

The histologic evidence of the destruction of erythrocytes by phagocytic cells of the spleen naturally suggests the possibility that these cells may liberate a hemolytic substance capable of acting either intracellularly or extracellularly. Could such a free hemolysin in the spleen be demonstrated it would at once explain the decreased tendency to jaundice in the splenectomized animal and would give some basis for splenectomy in the hemolytic anemias. The evidence presented in support of such a contention appears, on the whole, somewhat contradictory.

Banti, an adherent of the view that the spleen has a hemolytic function, bases his support upon the observation that the red blood-cells in the splenic vein show a decreased resistance to hypotonic salt solutions and upon the finding that fresh extracts of spleen contain a cyto-hemolysin. These observations, however, have not been confirmed by other workers.

According to the work of Krumbhaar and Musser the differences observed between the arterial and venous blood of the spleen are within the limits of error inherent in the methods used. In fact, some investigators (Chalier, Gabbi) have come to exactly the opposite conclusion, namely, that splenic vein blood is more resistant than the arterial blood. There is, therefore, little ground for the assumption that erythrocytes, in their passage through the spleen, are so acted upon by some unknown substance as to become more susceptible to hemolysis.

Nor is there uniformity of opinion concerning the hemolytic power of splenic extracts. Whereas Nolf, Weill, Banti(*b*)(*d*)(*c*) and Furno find extracts of the normal spleen to have a hemolytic action greater than that of other organs, Iscovesco and Zacchiri, Achard, Foix, and Salin, and Widal, Abrami, and Brulé, as well as Krumbhaar and Musser, Jr., fail to find any hemolytic action in fresh splenic extract. They are, therefore, inclined to regard the recorded instances of hemolytic action as due to autolysis or bacterial decomposition of the spleen.

Notwithstanding that hemolysis in the normal spleen cannot be demonstrated, it has been maintained that this does not exclude the possi-

bility that it exists and that hemolysis is active in some diseased conditions of the organ. But the evidence thus far obtained does not support such a contention. Thus Antonelli, Kahn, and Robertson(*a*) have not been able to demonstrate that the extracts obtained by them from the spleens of patients with hemolytic anemias possessed any hemolytic activity in vitro.

Again it has been held by some investigators that in the anemias characterized by hemolysis, there is at large in the blood a powerful hemolytic agent which is soluble in alcohol and ether, and which has been shown to diminish in amount following removal of the spleen. As a result of the work of Joannovics and Pick, of Eppinger(*b*)(*c*), and of King, attention has been more especially directed to the unsaturated fatty acids. Both Eppinger and King studied the fat content of the blood of normal and splenectomized animals and of a number of patients suffering from diseases characterized by hemolysis. According to their results, the blood of the dog after splenectomy shows an increase of the total fats and a decrease of the unsaturated fatty acids (lowering of the iodin figure). These results naturally raise the question of the possible influence of the unsaturated fatty acids in affecting the conditions of hemolysis after splenectomy and give significance to the observation of Eppinger that in a variety of clinical conditions characterized by excessive hemolysis, there occurs an increase in the unsaturated fatty acids of the blood, which after splenectomy sinks to normal. Such findings, if substantiated, might explain the increased resistance of the red blood-cells and the lessened tendency to hemolysis which often attends splenectomy in the hemolytic anemias. Dubin and Pearce, however, conclude from their careful experiments that splenectomy has no influence on the blood fat, but they feel, nevertheless, that this hypothesis is sufficiently attractive to justify, in view of the contradictions between their work and that of Eppinger and of King, a delayed opinion in the hope that further experiments may throw more light on this complex problem.

Some confusion concerning the regulatory function of the spleen has arisen because of the divergent results following the removal of the normal and abnormal spleen. Thus, both the blood crisis and the rise in the red blood-cell count which so frequently follows splenectomy for splenic disease, has been shown to be practically absent after removal of the normal spleen. Such a discrepancy may be due to a difference in the conditions which prevail. In one instance an abnormal spleen is removed under abnormal conditions of the blood, whereas in the other a normal spleen under normal conditions.

Many reasons for this paradox have been given. One probable and very attractive explanation is that in disease the improvement is due to the removal of an agent which both causes *hemolysis* and *depresses* bone-marrow function, whereas the anemia following normal splenectomy is

due to a loss of a normal stimulus to blood-formation. Then, too, the divergent results may be better explained if it be remembered that removing the spleen takes away only one organ of a system composed of liver, spleen, lymph nodes, and bone-marrow, and it is not unlikely that the interrelations which exist in the system may at times bring into play compensations of the greatest importance in determining the degree of blood destruction and regeneration.

Metabolism in Diseases of the Blood

A. Basal Metabolism in Anemia and Leukemia.—A great impetus to the study of basal heat production and respiratory metabolism in blood diseases followed the development of improved methods of direct and indirect calorimetry. Critical reviews of the earlier and the more recent work on this subject have been written by Strauss(*e*), Mohr(*i*), Meyer and Du Bois, Murphy, Means and Aub and Tompkins, Brittingham and Drinker.

Experimental and Clinical Observations.—Studies of the basal metabolism in animals have been limited, for the most part, to posthemorrhagic anemia. Bauer was among the first to show that the withdrawal of a considerable quantity of blood, amounting to 20 to 28 per cent of the calculated blood volume, may result in a lessened oxygen consumption and a diminished carbon dioxid production on the day following the bleeding. As a result of these experiments, the view became prevalent that a paucity of hemoglobin seriously impaired the oxidation processes and lowered the metabolic functions of the body. Subsequent investigations, however, proved that this hypothesis was incorrect inasmuch as no permanent departure from the normal metabolism could be demonstrated following blood-letting in animals. Finkler, and Pembrey and Gürber, for instance, found the respiratory metabolism in experimental secondary anemias normal and Delchef normal or slightly diminished; whereas, Frédéricq, Lukjanow, and Hári(*b*) demonstrated the existence of a somewhat elevated metabolism. The increase noted by the last three investigators is not striking. Frédéricq, who measured the heat production with the D'Arsonval compensation calorimeter, obtained results which have been shown to be well within the experimental error. Lukjanow found a 10 per cent increase in oxygen consumption immediately after the withdrawal of blood, but this did not persist on the day following the bleeding. And only once did Hári, using a Rubner calorimeter, find an increase of 12 per cent in the heat production of a dog after bleeding. It appears, therefore, that the variations noted by different observers are not significant, and that the tendency is distinctly toward a normal metabolism in posthemorrhagic anemia. Such diversity of results as have been

recorded may be attributed to lack of uniform and adequate precautions in regard to food, muscular activity and apparatus,—factors which are known to influence greatly the results obtained by calorimetric methods.

Pettenkofer and Voit(*c*) were among the first to apply clinical calorimetry to the study of blood conditions in man. They investigated the respiratory metabolism of a patient suffering from severe leukemia and found the gaseous exchange almost identical with that of a healthy individual taking the same diet. This pioneer experiment stimulated the later studies on this subject. Notable contributions on basal heat production in anemia and leukemia have been made by Magnus-Levy(*c*)(*g*), Kraus (*b*), Bohland(*a*), Thiele and Nehring, Grafe(*e*)(*f*)(*i*), Rolly, Meyer and Du Bois, Murphy, Means and Aub, and Tompkins, Brittingham and Drinker.

A comparison of the results of these different workers is rendered difficult on account of lack of uniformity in the experimental conditions, and in the normal standards of comparison used. Kraus and also Bohland, for instance, studied their patients under conditions which are now known to increase metabolism. The former neglected to have his patients at rest, and the latter disregarded the metabolism-accelerating influence of food. Notwithstanding such sources of error, some comparison of results has been made possible by Meyer and Du Bois and by Murphy, Means and Aub, who have recalculated the basal metabolism on certain clinical anemias and leukemias studied prior to their work on the basis of Mech's formula for surface area and the normal of 34.7 calories per square meter per hour.

The respiratory metabolism of *secondary anemia* and *chlorosis* has been studied by Kraus, Magnus-Levy(*g*), and Thiele and Nehring. When the figures for oxygen absorption which Kraus found in secondary anemia and chlorosis are expressed in terms of calories, the metabolism is abnormally high. This increase in calorific output may have been due, as previously mentioned, to the fact that these investigators permitted their patients to sit during the observation.

Magnus-Levy's results do not exceed the normal limits; whereas Thiele and Nehring report a normal metabolism for secondary anemia, but diminished or on the lower border of normal for chlorosis.

The results of various workers are more in agreement, however, as regards the basal heat production in *pernicious anemia.* Magnus-Levy and Kraus both found the metabolism increased in this type of anemia, the degree above normal varying from four to seventeen per cent. Basing their computations on modern standards (linear formula), Meyer and Du Bois found in their patients with pernicious anemia a metabolism on the upper limits of normal in mild cases, while in two severe cases the demand for oxygen was from seven to thirty-three per cent above the normal average. Greater irregularity in results was found by Tompkins,

TABLE 1.

BASAL METABOLISM IN CASES OF SECONDARY ANEMIA COLLECTED FROM THE LITERATURE

Observer	Patient	Hb. Per Cent	R.Q.	Calories per Sq. M. per Hour Meeh's Formula	Per Cent Above or Below Normal
Kraus, F.	L.S.	25	0.752	40.73	+ 17
Kraus, F.	L.S.	25	0.763	39.48	+ 14
Kraus, F.	L.S.	25	0.746	43.99	+ 27
Magnus-Levy	G.S.	..	0.860	33.77	— 3
Magnus-Levy	W.R.	..	0.779	37.27	+ 7
Magnus-Levy	B.L.	..	0.775	30.53	— 12
Thiele and Nehring	B.	..	0.877	35.59	+ 3
Thiele and Nehring	B.	..	0.850	34.53	— 0.5
Thiele and Nehring	B.	..	0.864	36.41	+ 5

Rearranged from Table by Meyer, A. L., and Du Bois, E. F., *Arch. Int. Med.*, 1916, xvii, 974.

Brittingham and Drinker. Their patients with pernicious anemia showed partly a normal metabolism, and in part one above and below the normal. In general, they found that the most severe cases showed a metabolism beyond normal limits in either direction, and that the long standing chronic cases gave a diminished, while the recent and more acute cases an elevated metabolism. Since two of the patients studied had elevated temperatures, and two others had complications in the larger organs, it is

TABLE 2.

BASAL METABOLISM IN CASES OF CHLOROSIS COLLECTED FROM THE LITERATURE

Observer	Patient	Hb. Per Cent	R.Q.	Calories per Sq. M. per Hour Meeh's Formula	Per Cent Above or Below Normal
Kraus, F.	V.H.	45	0.710	41.17	+ 19
Kraus, F.	V.H.	45	0.735	44.29	+ 28
Magnus-Levy	I.G.	..	0.806	34.01	— 0.2
Magnus-Levy	M.W.	..	0.794	36.68	+ 7
Thiele and Nehring	R.	85	0.902	31.76	— 8
Thiele and Nehring	R.	85	0.805	31.21	— 10
Thiele and Nehring	R.	85	0.858	31.97	— 8
Thiele and Nehring	P.	55	0.925	27.98	— 19
Thiele and Nehring	P.	55	0.800	27.89	— 19
Thiele and Nehring	P.	55	0.805	28.61	— 17
Thiele and Nehring	P.	55	0.779	29.63	— 15
Thiele and Nehring	P.	55	0.825	28.84	— 17
Thiele and Nehring	P.	55	0.806	29.03	— 16

Rearranged from Table by Meyer, A. L., and Du Bois, E. F., *Arch. Int. Med.*, 1916, xvii, 974.

not unlikely that in these instances the increased metabolism may be attributed, in part at least, to influences other than the anemia.

It is evident from this review that the results recorded in the literature concerning the metabolism in anemia show some variations. On the whole, however, experimental and clinical observations support the view that an anemic individual requires and consumes at least the same quantity of oxygen, and consequently produces the same number of calories as a healthy person; and that in certain of the severe anemias an increase of the respiratory metabolism and basal heat production may be observed.

The literature contains only a few observations on the basal metabolism of patients suffering from *leukemia*. Of the studies recorded those of Kraus, Magnus-Levy(*c*), Grafe(*e*), and Murphy, Means and Aub merit discussion. All these workers are agreed that in both forms of leukemia there is invariably a marked rise in the basal metabolism expressed in terms of body surface area. This elevation in basal heat production has been found about equal in both the lymphatic and splenomyelogenous types of the disease. Murphy, Means and Aub have calculated the average increase over the normal in eight cases of lymphatic leukemia recorded in the literature to be 52 per cent; and in five patients of myelogenous type, 44 per cent. Their own patient with chronic lymphatic leukemia showed a rise of 44 per cent above the average figure for normal men of that age.

Compensatory Factors in Anemic States.—The finding of a normal or augmented metabolism in anemic states has led to considerable speculation concerning the manner in which the body requirements of oxygen are met in the presence of a reduction of hemoglobin. Normally

TABLE 3

Basal Metabolism in Cases of Pernicious Anemia Collected from the Literature

Observer	Patient	Hb. Per Cent	R. Q.	Calories per Sq. M. per Hour Meeh's Formula	Per Cent Above or Below Normal
Kraus, F.	A.D.	30	0.710	37.52	+ 8
Kraus, F.	A.D.	30	0.709	40.55	+17
Magnus-Levy	M.	..	0.813	38.87	+12
Magnus-Levy	W.	..	0.738	36.17	+ 4
Meyer and DuBois	D.V.	25	0.803	37.50	+ 8
Meyer and DuBois	A.K.	20	0.839	42.99	+24
Meyer and DuBois	A.K.	20	0.835	41.31	+19
Meyer and DuBois	M.C.	23	0.787	48.07	+33
Meyer and DuBois	M.C.	21	0.865	39.61	+ 7
Meyer and DuBois	B.D.	44	0.830	33.53	+ 2
Meyer and DuBois	D.O.	40	0.767	36.78	+ 6

Rearranged from Table by Meyer, A. L., and Dubois, E. F. *Arch. Int. Med.*, 1916, xvii, 974.

TABLE 4

BASAL METABOLISM IN CASES OF LEUKEMIA COLLECTED FROM THE LITERATURE

Observer	Type	Patient	Calories per Sq. M. per Hour (Meeh)	Per Cent Above or Below Normal	Total Leukocytes	P. M. N. Per Cent	Lympho-cytes Per Cent	Total R. B. C.	Hb. Per Cent
Grafe	Lymphatic	T.S. 1a	68.7	+123	820,000	10	89	3,600,000	40
Grafe	Lymphatic	T.S. 1b	52.0	+ 69	205,000	10	89	.....	..
Grafe	Lymphatic	T.S. 1c	48.7	+ 58	200,000	5	95	2,400,000	30
Grafe	Lymphatic	G.K. 2	36.8	+ 19	40,000	28	72	4,800,000	90
Grafe	Lymphatic	C.L. 3a	44.5	+ 55	130,000	4	96	.....	..
Grafe	Lymphatic	C.L. 3b	46.9	+ 63	165,000	2	98	3,640,000	75
Grafe	Lymphatic	M.T. 4	65.0	+ 87	32,000	12	87	3,800,000	70 to 75
Grafe	Lymphatic	M.D. 5	49.8	+ 62	170,000	2	98	3,800,000	80
Grafe	Myelogenous	F.H. 6	53.2	+ 53	140,000	95	5	4,700,000	60
Grafe	Myelogenous	M.H. 7	49.8	+ 54	180,000	95	5	2,600,000	55
Grafe	Myelogenous	H.B. 8	42.3	+ 22	230,000	98	2	.....	75
Magnus-Levy	Lymphatic	J.	45.1	+ 30	.....	..	..	.....	..
Kraus, F.	Splenomyelogenous	M.B.	48.7	+ 58	450,000	..	..	2,800,000	50
Kraus, F.	Splenomyelogenous	M.B.	46.4	+ 51	.....	..	..	.....	..
Kraus, F.	Splenomyelogenous	M.B.	45.8	+ 49	.....	..	..	.....	..
Kraus, F.	Splenomyelogenous	W.K.	47.8	+ 38	230,000	..	..	2,400,000	45
Kraus, F.	Splenomyelogenous	W.K.	46.7	+ 35	.....	..	..	.....	..
Kraus, F.	Splenomyelogenous	W.K.	49.4	+ 42	.....	..	..	.....	..
Kraus, F.	Lienalis	S.W.	49.7	+ 54	345,000 to 425,000	..	..	2,990,000 to 2,720,000	50 to 45
Kraus, F.	Lienalis	S.W.	49.2	+ 52	345,000 to 425,000	..	..	2,990,000 to 2,720,000	50 to 45
Bohland, K.	Lienalis	H.	51.8	+ 60	.....	..	..	.....	..
Bohland, K.	Lienalis	H.	57.8	+ 79	.....	..	..	.....	..
Bohland, K.	Lienalis	H.	56.7	+ 76	.....	..	..	.....	..
Bohland, K.	Lienalis	H.	54.8	+ 70	.....	..	..	.....	..
Bohland, K.	Lymphatic	R.	55.3	+ 59	.....	..	..	.....	..
Bohland, K.	Lymphatic	R.	42.1	+ 21	.....	..	..	.....	..
Bohland, K.	Lymphatic	R.	42.9	+ 24	.....	..	..	.....	..
Bohland, K.	Lymphatic and Lienalis	L.	48.0	+ 38	.....	..	..	.....	..
Bohland, K.	Lymphatic and Lienalis	L.	43.7	+ 26	.....	..	..	.....	..
Bohland, K.	Lymphatic and Lienalis	L.	42.9	+ 24	.....	..	..	.....	..
Bohland, K.	Lymphatic and Lienalis	L.	59.0	+ 70	.....	..	..	.....	..
Bohland, K.	Lymphatic and Lienalis	L.	47.3	+ 36	.....	..	..	.....	..
Murphy, Means and Aub	Lymphatic	A.W.	57.1		55,000	..	..	.....	..
Murphy, Means and Aub	Lymphatic	A.W.	55.9		.....	..	..	.....	..
Murphy, Means and Aub	Lymphatic	A.W.	53.2		.....	..	..	.....	..
Murphy, Means and Aub	Lymphatic	A.W.	53.4		.....	..	..	.....	..
Murphy, Means and Aub	Lymphatic	A.W.	47.7		.....	..	..	.....	..

Rearranged from Table by Murphy, J. B., Means, J. H. and Aub, J. C., *Arch. Int. Med.*, 1917, xix, 892.

the supply of oxygen to the tissues is beyond the immediate requirement. In anemia, when the hemoglobin content is low and the volume per cent of oxygen is correspondingly diminished, the consumption of oxygen remains normal, or may even be above the normal. Many views are held concerning the compensatory mechanism at work.

It has been suggested that a more liberal supply of blood to the tissues may be favored by a greater respiratory volume. Such an increase in the depth of respirations has been noted by Jürgensen, and Kraus(*b*). But since the tension of oxygen in the alveolar air of anemic individuals is normally sufficient to saturate about 96 per cent of the hemoglobin in the blood, it is difficult to see that much would be gained by increased pulmonary ventilation.

Nor has it been determined that the respiratory compensation in chronic anemia resides in the blood itself. It was at one time thought that the hemoglobin of anemic blood might differ from that of normal blood in its power to carry oxygen. Such a conception, however, has been rendered improbable by a comparison of the specific oxygen capacity of normal and anemic bloods (Butterfield, Peters).

There are two other ways in which the anemic patient may carry on his gaseous metabolism in spite of a marked reduction in hemoglobin. Either the rate of the circulation is increased (Mohr(*e*), Plesch(*a*)), so that the diminished amounts of hemoglobin are used more frequently for transporting oxygen, or else the oxyhemoglobin which reaches the tissues gives up unusually large amounts of oxygen, the blood returning to the heart in various degrees of asphyxia (Kraus, Mohr, Morawitz).

It has not as yet been determined with certainty which of these two methods is the more important in the chronic anemias of man. By an indirect method of determining the total blood flow in man, Plesch found that this was always increased in anemias in approximate proportion to the severity of the anemia. According to his view, the anemic individual compensates for his lack of hemoglobin almost entirely by maintaining a more rapid circulation. Some objection to this view has come from the observation that it is uncommon to encounter marked hypertrophy of the heart even after long-continued severe anemias, which would be the case if the heart continually did an increased amount of work.

Concerning the degree to which the hemoglobin gives up oxygen to the tissues of anemic patients, there is likewise considerable difference of opinion. Mohr found a marked reduction in the oxygen content of venous blood taken from animals that had been rendered anemic by hemorrhage, indicating that the hemoglobin had given up an unusually large prooprtion of its oxygen during its passage through the tissues. A similar observation was made by Morawitz and Röhmer, whereas Plesch

found no marked variations from the normal in his gas analyses of alveolar air.

Most workers are inclined to the view that the increased muscular work required by the more rapid respiration and accelerated heart rate is sufficient to cause such increases in metabolism as have been observed in the anemias. Indeed, it has been shown that therapeutic measures, such as transfusion, by reducing the heart rate and respiration to normal, may restrain the muscular compensation and thereby lower the basal metabolism to normal limits (Tompkins, Brittingham and Drinker). This phase of the subject will be discussed more fully when the effects of various therapeutic agents upon the metabolic rate are considered.

The Cause of High Metabolism in Anemia and Leukemia.—A number of workers have explained the high metabolism observed in anemia and in leukemia by causes which are not definitely compensatory. Thus, Grafe(*e*) believes that the extra heat production may be attributed to the increased metabolism of young, nucleated corpuscles and unusual numbers of white blood-cells.

Grafe and also Eberstadt attempted to correlate the blood-forming ability of anemic animals with the metabolism. They found that rabbits with exhausted marrow from hemorrhagic anemia due to phenylhydrazin injections had a diminished metabolism, while those anemic but with normal marrow showed normal metabolism. The same relationship has been found by Grafe(*i*) to exist in certain forms of clinical anemia. In two of the most severe cases of pernicious anemia with signs of marrow insufficiency, he found the lowest values in his series, and a third case gave a much higher metabolism during a blood crisis, than subsequently when regeneration was less active. A recalculation of these results by later workers (Tompkins, Brittingham and Drinker) using Meeh's formula seems to bear out Grafe's contention. According to these computations, the first two patients had a metabolism on the lower border of normal, while the third case had an elevated metabolism during the crisis, whereas during the period of moderate regeneration the heat production became normal.

Rolly's experimental and clinical observations are not in accord with those of Grafe. Computations of Rolly's figures on the basis of Meeh's formula show a metabolism which is considerably elevated not only in a patient with pernicious anemia, but also in one with aplastic anemia due to carcinoma.

Although there is some support for the view that nucleated red blood-cells constitute a considerable mass of young tissue which consumes more oxygen and produces more carbon dioxid (Morawitz(*a*)), yet the evidence that these developing cells alone are responsible for the heightened basal metabolism in certain anemias is still incomplete.

The greater calorific output so constantly present in the leukemias

has been likewise attributed to the very active metabolism of young white cells. But it is doubtful whether the high metabolism is entirely due to the leukocytes. Grafe's experiments on the metabolism of blood do show an increased oxygen consumption in leukemic blood. It has been estimated, however, that only 10 per cent of the total oxygen consumption can be referred to the leukocytes, whereas the rise in the basal metabolism may range at times from 40 to 60 per cent. Murphy, Means and Aub have plotted the leukocyte counts and the heat production noted in their own patient with chronic lymphatic leukemia, as well as in the recorded cases (Table 4) to see whether there was any relation between the leukocyte count and the level of the metabolism. They found a certain parallelism to exist in individual cases, the fall in leukocytes being always much greater than that in the metabolism (Fig. 3). Among different cases, however, there was no such relation. But the lack of such relationship does not, according to these workers, disprove Grafe's theory, since the determining factor is the rate of production of white blood-cells and not their total number.

Protein Metabolism.—*The Nitrogen Balance in Anemia.*—The earliest work on the changes in protein metabolism in the anemic organism was carried out on animals. Although many of these studies were made by very defective methods, according to present-day views, the results obtained appear nevertheless to coincide with those of later workers.

Bauer was the first to study the effect of hemorrhage on the nitrogen elimination in the dog. In a well-nourished animal, in nitrogen equilibrium, he found the average daily elimination of nitrogen for four days before bleeding to be 16.6 grams. After a hemorrhage amounting to 2 per cent of the body weight, the nitrogen output for three days following the bleeding averaged 19.9 grams. By the sixth day, the nitrogen balance was again restored, the average elimination between the sixth and ninth day being 16.1 grams nitrogen. In the fasting animal, Bauer obtained essentially similar results. From an average nitrogen output of 3.27 grams before bleeding, the figure rose to an average of 4.75 grams after blood-letting. These results lead Bauer to the conclusion that external hemorrhage temporarily increases protein catabolism, and that the effect is relatively greater in fasting animals than in well-nourished ones.

With the exception of Ascoli and Draghi, who demonstrated a decreased rather than an increased protein catabolism in acute posthemorrhagic anemia, the conclusions of subsequent investigators coincide, in the main, with those of Bauer. Jürgensen, for instance, working on fasting dogs, in nitrogen equilibrium, found that whereas small hemorrhages produced little change, losses of blood equal to 1.2 per cent to 3.4 per cent of the body weight result in an increased urea elimination in the urine.

It is of interest that the more carefully planned observations of later

workers agree, on the whole, with those of Bauer and of Jürgensen, notwithstanding the criticism to which the earlier experiments are subject because of the shortness of the periods of observation, the crudeness of the methods employed, and the failure to take adequate account of the amount and composition of the food taken. Thus Hawk, and Gies found in well-nourished animals, in weight and nitrogen equilibrium, and fed continuously on a diet of constant composition, a temporary increase in the elimination of nitrogenous products in the urine. Similarly, Haskins (*a*) noted a decided rise in the amount of total nitrogen excreted on the two days following hemorrhage. Such a primary rise in nitrogen elimination has been observed also by Kerr, Hurwitz and Whipple(*a*)(*b*)(*c*) in their studies on the regeneration of the blood proteins. For a few days following the shock of plasmapharesis, there was a primary rise in nitrogen elimination. In some instances, the initial increase in nitrogen output after bleeding may be followed by nitrogen retention (Fuchs).

Buell(*b*) in a recent study of the effect of hemorrhage on nitrogenous excretion in the pig found that only where the nitrogen eliminated represented endogenous metabolism, was there indication of an increased output. This observation harmonizes well with the results of experiments on fasting animals. The fact that hemorrhage results in greater nitrogen elimination in fasting animals has been interpreted to mean that after protein starvation, the cells themselves must furnish much of the new material needed to restore the blood and keep its composition constant. Thus the increased autolysis of body tissue and the greater activity of the blood-forming organs results in a correspondingly greater excretion of the end-products of protein metabolism than is the case when extracellular sources are drawn upon.

Most of the metabolism experiments indicate, therefore, that after bleeding there is a relatively slight and only temporary increase in nitrogen elimination. The influences which may bring about this stimulation of protein catabolism are probably numerous and complex. At least three factors must play a part in the production of the effects noted. In the first place, loss of blood, if considerable, must at once affect the nutrition of the higher centers concerned in the chemical and physical regulation of certain body functions; secondly, hemorrhage, by greatly stimulating the activity of the blood-making organs, results in an increase of the normal waste products of these organs; and lastly, loss of blood influences profoundly the exchange of fluids between the blood and the tissue spaces. It is not unlikely that the withdrawal of fluid from the tissue spaces which occurs after hemorrhage, to replace the volume of the blood, leads to the accumulation in it of abnormal amounts of waste products,—ammonia components, creatin, and purin bases, which are eliminated by the kidneys.

A considerable diversity of opinion prevails, however, as regards the

effect of hemorrhage on protein metabolism in the secondary anemias in man. These discordant results may be due, in part at least, to the difference in the effects produced by external and by internal hemorrhage upon nitrogen excretion.

Ascoli and Draghi, in a study of five patients following the removal of from 200 to 500 c.c. of blood, found evidences of increased rather than decreased protein catabolism in three of the five patients. Their results have been criticized, however, because of the abnormality of the subjects, the inadequate control of the food intake, and the shortness of the periods of observation. Strauss(*e*), on the other hand, studied the effects of bloodletting (150 to 200 c.c.) upon the metabolism of individuals in nitrogen equilibrium. None of the four patients observed by him showed any increase in nitrogen output as a consequence of the withdrawal of blood. However, in four out of seven patients with gastric hemorrhage he found high values for nitrogen in the urine. This finding is opposed to the view of von Noorden, who failed to find a greater excretion of nitrogen, either on the day of the hemorrhage, or on the days immediately succeeding it. That certain internal hemorrhages may at times be associated with an increase in the elimination of nitrogen appears probable from the work of some investigators, who attribute the high numerical values for nitrogen in the urine of patients with gastric hemorrhage, to the absorption and decomposition of large quantities of blood in the intestine (Strauss).

The results of studies on the nitrogen metabolism of patients with chlorosis are less conflicting. The view held by von Noorden that protein metabolism is practically normal in ordinary cases of chlorosis has received support from the experimental work of the majority of investigators, more particularly of Vannini, who found only a slight retention of nitrogen in three instances, approximate nitrogenous equilibrium in one instance, and a slight nitrogen loss in another instance. These metabolic studies on chlorotic patients do not support the view that chlorosis is due to the action of some toxic factor, inasmuch as the effect of such an agent usually is to destroy tissue protein, which would be indicated by a nitrogen loss.

In the anemia of Banti's disease Umber(*b*) demonstrated a pathological decomposition of protein, which, because of its disappearance following splenectomy, he attributed to a toxic agent produced in the diseased spleen. According to this worker, the same toxic factor produced both the anemia and the metabolic changes observed. Other investigators (Müller(*a*), Luce, Lommel(*c*), Grosser), however, have failed to confirm this observation.

A number of studies have been made on the protein metabolism in the *hemolytic anemias* of known and unknown etiology. Von Noorden(*a*) (*b*)(*d*) was the first to carry out accurate observations on the protein decomposition in pernicious anemia. His experiments, in which the

essential requirements for careful metabolic work were fulfilled, do not support the findings of some of the earlier investigators, who report a pathological destruction of protein in this disease. Von Noorden found, on the contrary, that some of the patients may show a tendency to retain nitrogen. His conclusions have, in the main, received support from the subsequent contributions of von Stejskal and Erben(*b*), Strauss, Halpern, and Bloch. In an experiment extending over six days, Bloch found in one patient with pernicious anemia a retention of nitrogen amounting to 3.08 grams per day on an intake of 17.8 grams, and in another instance, a retention of 1.08 grams on an intake of 17.23 grams of nitrogen. Positive nitrogen balances of this grade may be attributed either to previous undernutrition (Bernert and von Steyskal), or what is more likely in these particular instances, to forced protein feeding, which as Mosenthal(*d*) has pointed out, may lead to the increased assimilation of nitrogen in patients with pernicious anemia.

Minot(*a*), on the other hand, in a study of the nitrogen metabolism in pernicious anemia before and after splenectomy, reports an average daily nitrogen loss of 0.78 gram before and a slightly positive balance of 0.6 gram after operation. This conversion of a negative into a positive nitrogen balance in pernicious anemia has not been confirmed by Pepper and Austin(*c*). These workers found the nitrogen balance slightly positive both before and after splenectomy.

Rosenqvist, who carried out extensive studies on the protein metabolism in pernicious and dibothriocephalus anemia obtained results which are to some extent opposed to those of other investigators. He found considerable fluctuation in the nitrogen balance in pernicious anemia, periods of increased nitrogen loss alternating with periods of nitrogen retention. Interesting in this connection is the observation of Rosenqvist that some of the eighteen patients with bothriocephalus anemia studied showed a well-marked loss of nitrogen only during the presence of the tapeworm in the body, whereas after its extrusion, a retention of nitrogen was usually demonstrable.

Strauss and Umber have suggested that the fluctuations in the nitrogen balance noted by Rosenqvist might have been due to the employment of faulty methods, as well as to functional disturbances of a temporary nature in the alimentary tract and in the kidneys. It is not unlikely that a severe anemia might lead to variations in the amount of material absorbed per day, and in certain instances, more or less protracted disturbances of renal function may result from the anemia, which would give rise to irregularities in the excretion of nitrogen such as are sometimes found in patients suffering from renal disease (Christian).

The nitrogen metabolism in *congenital hemolytic icterus* has been studied by McKelvy and Rosenbloom, and by Goldschmidt, Pepper and Pearce. During a period of five days the former workers found a loss of

4.06 grams of nitrogen, which may, according to them, be the result of a possible toxogenic destruction of protein. In their patient, on the other hand, Pearce and his co-workers found a slightly positive nitrogen balance. In experimental hemolytic anemia produced by hemolytic serum, Pearce, and Jackson noted an increased output of total nitrogen, rest nitrogen, purins, and phosphorus. These experimental results are of interest because, as these workers point out, the changes caused by hemolytic serum—anemia, jaundice, and cell degeneration—represent as close an approach, aside from chronicity, to conditions in congenital hemolytic jaundice as can be brought about experimentally. These studies are suggestive and give some support to the view that a toxic destruction of tissue may take place in the hemolytic anemias.

A review of the literature of this subject indicates, therefore, that even the most severe types of chronic anemia may often run their course for a considerable period without injury to the body protein; but that under certain conditions, a pathological increase in the excretion of nitrogen may at times occur in the course of severe anemias as a result of the toxic destruction of protein. That this may explain the increased protein destruction in the severe anemias of known etiology appears not unlikely. Thus Rosenqvist has shown that the hemolytic lipoid extracted by Tallqvist from the fish tapeworm acts destructively not only upon the red blood-corpuscles, but also upon the protoplasm of other tissues, and, according to Bohland a similar condition may be present in the anemia of anchylostomiasis.

That other poisons may also cause a destruction of body tissue protein has gained support from the experiments of Whipple and his co-workers, who demonstrated a great rise in the urinary nitrogen in animals after the injection of a toxic proteose obtained from closed intestinal loops or following the absorption of protein split-products either from such loops or from inflammatory exudates.

The Nitrogen Balance in Leukemia.—The nitrogenous metabolism in acute and chronic leukemia has been studied by a number of investigators. An accurate estimation of the results of many of the earlier researches is rendered difficult by the shortness of the periods of observation, the lack of accurate determinations of the food intake, and the presence of such complicating factors as fever, hemorrhage, and the like. Of the studies recorded in the literature, those of Magnus-Levy(*c*), von Stejskal and Erben(*a*), Taylor(*b*), Musser and Edsall, Edsall(*b*), Goodall, and Murphy, Means and Aub permit of some definite conclusions. These studies seem to show fairly definitely that there is, in chronic leukemia, no increase in the nitrogenous metabolism at all comparable with that in the respiratory metabolism. There is either a slight retention, a slight loss, or a nitrogen balance.

Some differences have been found to exist in the two forms of chronic

leukemia. In a patient with chronic myelogenous leukemia, von Stejskal and Erben found the nitrogen loss much greater than in the lymphatic form, and Murphy, Means and Aub could maintain their patient with chronic lymphatic leukemia in nitrogen equilibrium on a nitrogenous intake of 13 to 15 grams per day. It has been suggested that the greater protein combustion in myelogenous leukemia may be due to richness of the polymorphonuclear leukocytes in autolytic enzymes, which gives these cells greater metabolic activity than the lymphocytes.

TABLE 5

NITROGEN AND PURIN METABOLISM IN A PATIENT WITH CHRONIC LYMPHATIC LEUKEMIA

Name and Date	Food Carbohydrates	Fat	Food N	Urine N	Excreta * N	Nitrogen Balance	Uric Acid	Purin
	Grams	Grams	Grams	Grams	Grams	Grams	Grams	Grams
Anthony W								
4-19-16	144	110	11.0	10.2	11.3	—0.3	.....	.....
4-20-16	212	138	14.9	10.3	11.8	+3.1	0.522	0.014
4-21-16	215	132	13.7	11.8	13.2	+0.5	0.520	0.017
4-22-16	214	144	15.2	10.4	11.9	+3.3	0.489	0.006
4-23-16	196	142	15.5	10.9	12.5	+3.0	0.500	0.005
4-24-16	175	128	14.2	12.0	13.4	+0.8	0.563	0.038
5-1-16	160	113	12.9	10.2	11.5	+1.4	0.569	0.016

* Excreta Nitrogen calculated as urine nitrogen plus 10 per cent of food nitrogen.
After Murphy, J. B., Means, J. H. and Aub, J. C.: *Arch. Int Med.*, 1917, xix, 902.

In acute leukemia, on the other hand, Magnus-Levy and also Edsall have noted an enormous increase in protein metabolism. The former observed repeatedly an elimination of nitrogen which exceeded the intake, in some instances, by as much as 40 grams per day; whereas Edsall reports a negative balance of 22.28 grams a day on a nitrogen intake of 7.25 grams.

It is possible that the great variations which different workers have found in the protein metabolism in the leukemias may depend, in part at least, upon the fluctuations which are known to occur in the course of the pathological processes of this disease. When it is considered how greatly the number of leukocytes, the size of the lymphatic organs, and the general condition of the patient may vary from time to time, it is not surprising that the excretion of the products of metabolic activity should show corresponding fluctuations. During the ordinary course of the disease, the total nitrogen elimination, as a rule, corresponds closely to the protein of the diet; while, during periods of rapid leukocyte formation or more especially during periods of rapid leukocyte destruction the change may be indicated by the nitrogen output.

Purin Metabolism.—The purin metabolism in anemia and leukemia has been extensively studied. This phase of metabolism is of particular

interest in these conditions, because of the well-established relationship between the excessive destruction of body cells and the increased elimination of purin bodies, and more especially of uric acid, in the urine. Since the amount of uric acid excreted is influenced by many factors, but more particularly by the methods used and the composition of the food, only those studies of the endogenous uric acid metabolism are of value in which the purin intake has been accurately controlled and the determinations made by reliable methods.

Experimental and Clinical Observations in the Anemias.—The effect of acute losses of blood on uric acid metabolism has been studied experimentally by Haskins(*a*) and by Buell(*b*), and in man by Strauss(*c*). Although it has been supposed that, on account of the autolysis of tissue protein caused by hemorrhage the uric acid output might show some increase, neither Buell nor Strauss could find any appreciable change in uric acid elimination after blood-letting. The increase noted by Haskins lasted only one day. In acute posthemorrhagic anemia following a gastric hemorrhage, on the other hand, Strauss and also Mohr(*e*) demonstrated high values for uric acid. In one instance, Strauss records a rise in the uric acid nitrogen from a minimum of 0.136 gram on the second day of the hemorrhage to an average output of 0.358 gram during the following fourteen days. In Mohr's patient, the uric acid excreted on the seventh day after the hemorrhage was about twice the normal figure. Where the anemia resulted from repeated small hemorrhages Strauss observed no changes in the uric acid output. It has been suggested that the increased excretion of purins following large internal hemorrhages might be due to the excessive decomposition and absorption of nucleoprotein resulting from the destruction of red cells.

Purin metabolism in the secondary anemia of *Banti's disease* has been studied by Umber(*b*). The diet was purin-free and a fully controlled metabolic study was made. Umber, in his studies, does not report uric acid output, but groups his findings under total purins, of which he found, in Banti's disease, a somewhat greater output before splenectomy than after.

The available studies of the nuclein metabolism on patients with *chlorosis* are subject to the criticism that there was no control of the purin intake in the food. Even though purins were ingested by the chlorotic patients studied the quantities of uric acid excreted by them were found only slightly higher than normal. Thus Von Noorden obtained 0.22 gram of uric acid nitrogen per day in a patient with severe chlorosis, while von Moraczewski(*b*) found in eleven cases an average value of 0.26 gram, a figure on the upper limits of normal. Similar results were obtained by Vannini.

In the *hemolytic anemias* wide fluctuations in uric acid elimination have been observed, but the general view appears to prevail that during

certain periods in the course of the diseases of this group, the elimination may be high. Thus Schmidt in two patients with severe anemia noted an increased elimination of purin nitrogen and Rosenqvist, as a result of his studies of pernicious anemia and bothriocephalus anemia, reports large outputs of uric acid, sometimes twice the normal. Pepper and Austin(*c*), on the other hand, found in their careful metabolic study of a patient with pernicious anemia, a uric acid output, which never exceeded normal limits (Table 6). Their interesting finding of a decrease of 22 per cent in the uric acid elimination after splenectomy will be considered later.

The observations of Rosenqvist on the uric acid metabolism in bothriocephalus anemia are of great importance because the toxic agent in this type of anemia is known. He found that after the extrusion of the tapeworm from the body, there is first an increased elimination of purins and then a return to the normal. This initial rise has been explained as the result of an increased metabolic activity of the blood and somatic cells following the removal of a toxic substance.

It is not improbable that some toxic factor may play a part also in the increased nuclein metabolism noted in *congenital hemolytic jaundice.* In one form of hemolytic icterus produced experimentally by the injection of hemolytic serum into animals, Jackson and Pearce found the elimination of purin bodies increased. Similarly, high figures for uric acid have been reported by Tileston and Griffen, McKelvy and Rosenbloom, and Goldschmidt, Pepper and Pearce, in patients with congenital hemolytic jaundice (Table 7). According to McKelvy and Rosenbloom, the large output of purin, noted in this disease, may be due to the greater formation of nucleoprotein resulting from the destruction of red cells. Pearce and his co-workers, however, are inclined to the view that the increased cellular metabolism is attributable, in part at least, to the toxic influence on the somatic cells of bile products. They point out that the sallow discoloration of the skin in the disease is indicative of the general dissemination of a substance absorbed directly or indirectly from the bile, the toxic action of which may explain the widespread cell disintegration with the resulting increase in the products of nuclein metabolism. The remarkable effect of splenectomy in decreasing the uric acid output in this disease almost to one-half the initial amount will be discussed in its proper place.

The Elimination of Uric Acid and Purin Bases in Leukemia.— Studies of purin metabolism in diseases of the blood have a particular interest in leukemia. In general, it might be expected that the enormous increase in the nucleoprotein-containing tissues and blood-cells, which occur in this disease, would give rise to a greatly increased catabolism of nucleins, with the consequent appearance of greater amounts of uric acid and of purin bases in the urine. Urinary findings, however, have been very variable in this respect. Whereas, some workers have noted a

greater uric acid elimination, and others have observed an increase in the purin bases, either with or without a uric acid increase, there are those whose results show the variations found in health. The reasons for these fluctuations will be considered later.

The few available metabolic studies carried out on patients with *acute leukemia* have led, on the whole, to some uniformity of result. The evidence points out only to a rapid destruction of body protein in the acute forms of leukemia, as indicated by the enormous loss of nitrogen in the urine, but also to an accelerated nuclein catabolism with increased elimination of uric acid. The careful observations both of Magnus-Levy (*c*) and of Edsall(*b*) support this view. The former studied three such patients on a purin-poor diet. In one of these, he found the uric acid nitrogen 2.91 grams two days before death, and in the other two patients observed over longer periods, he noted an average uric acid nitrogen excretion of 0.655 and 0.523 gram respectively.

In the chronic types of leukemia, this phase of metabolism has been more extensively studied. From a review of the literature of this subject, the conclusion may be drawn that, during the ordinary clinical course of the disease, the excretion of uric acid and the purin bases may be within normal limits, but that during periods of rapid leukocyte formation, and more especially during periods of rapid leukocyte destruction, the change may be indicated by fluctuations in the output of these bodies. Such fluctuations, however, do not always occur.

A comparison of the results obtained in the two forms of chronic leukemia are of interest. Both Magnus-Levy(*c*) and von Stejskal and Erben(*a*) among the earlier workers report higher values for uric acid nitrogen in the myelogenous than in the lymphatic form of leukemia. Thus von Stejskal and Erben record an output of 0.354 gram of uric acid nitrogen in a patient with myelogenous leukemia as compared with an elimination of only 0.232 gram in an instance of the lymphatic type. These observations have, in the main, received support from later investigators (Schmidt, Galdi, Rotky, Lossen and Morawitz, Goodall).

In Goodall's case of chronic myelogenous leukemia, there was a high endogenous uric acid elimination, but this showed marked variations, which had no relation to the total nitrogen excretion or to the rate of leukocyte destruction. This worker concluded, therefore, that the destructive process might be carried beyond the uric acid stage, and that under certain conditions, retention of uric acid might occur for the purpose of the new formation of leukocytes.

Certain it is that not all patients with chronic leukemia show an increased uric acid elimination. This is particularly true of the lymphatic form of the disease. With the exception of Wende, who reports a case of lymphatic leukemia with a uric acid excretion of 5 grams, most investigators (Henderson, Vas, Rzentkowski, Murphy, Means and Aub), who

have studied the nuclein metabolism in chronic lymphatic leukemia, have noted an output of uric acid which was normal or on the upper limits of normal.

In the paragraphs on the nitrogen metabolism in leukemia attention was called to a possible explanation of the variations observed. It is not unlikely that in this instance also the same natural fluctuations in the pathological processes and in the clinical course, which characterize this disease, may explain the variability of results obtained in the studies on the elimination of the purin bodies.

That no definite parallelism exists between the quantity of uric acid excreted and the number of circulating leukocytes appears fairly certain from the work of the majority of investigators (Mohr(*i*)). High values have been found associated not only with large numbers of leukocytes, but also with relatively small numbers. The same lack of parallelism has been observed between the degree of leukocytic disintegration produced by the röntgen-rays and by radium and the quantity of uric acid excreted in the urine. This aspect of the subject will receive fuller consideration in the paragraphs relating to the effects of the actinic rays on metabolism in blood diseases.

The Partition of Other Nitrogenous Constituents of the Urine.—The effect of anemia on the elimination of certain of the other urinary nitrogenous substances has been studied quite extensively. The main interest in these observations lies in the knowledge which they give concerning the influence of a paucity of hemoglobin on the synthesis of urea by the liver, the development of acidosis as indicated by the excretion of ammonia, and the metabolism of the amino-acids.

The results of the determinations of the partition of urinary nitrogen in experimental and clinical posthemorrhagic anemias are somewhat discordant. Observations on the influence of hemorrhage in animals upon the nitrogen partition have been made by Haskins(*a*) and more recently by Buell(*b*). After the removal of 250 c.c. of blood from a dog, Haskins noted a decrease in the urea and creatinin nitrogen, the former dropping 13.7 per cent and the latter 7.8 per cent; while the ammonia nitrogen increased to the extent of 11 per cent. Buell, on the other hand, observed no change in the elimination of urea, ammonia, and creatinin, the only difference noted being an increased output of creatin. The cause of this creatinuria is not quite clear. It may better be explained, according to Buell, by the occurrence of an alteration in the course of nitrogen metabolism following hemorrhage, rather than by the development of an acidosis, which does not, as a rule, follow hemorrhage.

In the acute and chronic posthemorrhagic anemias of man, the older work, reviewed by Strauss(*e*) and by Mohr(*i*), points to little variation from the normal nitrogen partition. The fluctuations which have been noted are all within the normal physiological limits. Occasionally, a high

output of ammonia was observed in these conditions, but this may be partly the result of such factors as inanition, and not therefore directly attributable to the anemia.

Observations on the nitrogen partition in *chlorosis* are not numerous. These have been analyzed by Vannini in his careful metabolic study of this disease. Great fluctuations in the percentage of urea and ammonia nitrogen are recorded by most workers. For urea the values found range from 83 to 92 per cent, and for ammonia from about 2 to 9.5 per cent of the total nitrogen. Although Vannini's figures are in accord with those

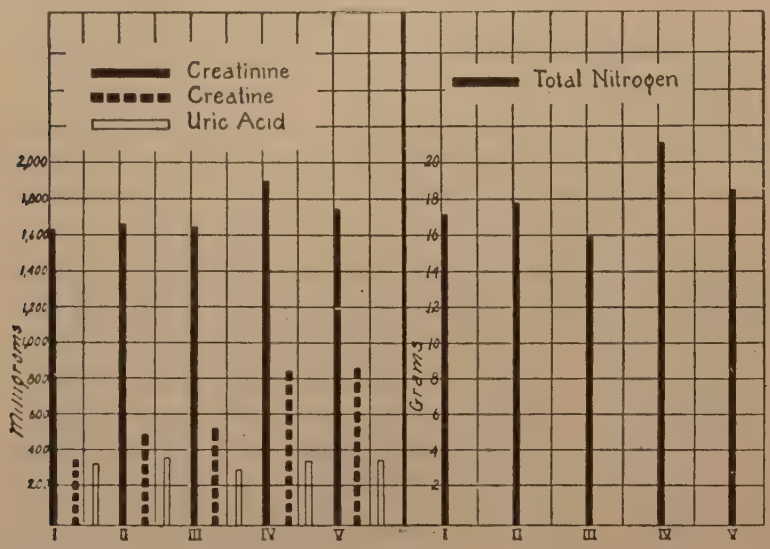

Fig. 3.—Effect of hemorrhage on the excretion of creatinin, creatin, uric acid and total nitrogen in the pig. The vertical lines represent the averages of the actual amounts excreted during various periods of the experiment. Line I represents the fore-period, Line II the period between the first and second hemorrhages, Line III the period between the second and third hemorrhages. (After Buell, M.V., J. Biol. Chem., 1919, xl, 75.)

of earlier observers so far as the percentage of urea nitrogen is concerned, his ammonia percentages are considerably lower than the average, ranging from 2.06 to 2.63 per cent.

Determinations by different workers of the various urinary nitrogen fractions in the *hemolytic anemias* are also lacking in uniformity. In a careful metabolic study of experimental pyrodin anemia in animals, Samuely(*a*) noted that as the anemia progressed the urea percentage fell from 86.3 to 72.14 per cent, whereas the ammonia and the amino-acid fractions increased.

In patients with *pernicious anemia,* a change in the partition of the nitrogenous substances in the urine has been observed only in exceptional cases. Minot(*a*) found a low urea percentage and a normal ammonia out-

put in a patient with pernicious anemia, whereas von Jaksch(*j*), and Halpern record a normal nitrogen partition of urea, ammonia, and amino-acids in a number of instances of severe anemia including some cases of bothriocephalus anemia. And Denis(*d*) in her study of two patients with pernicious anemia before and after splenectomy also reports normal variations in the output of creatin and creatinin.

Three complete metabolism studies of patients with hemolytic icterus are available for analysis. Tileston and Griffen in a patient with "chronic family jaundice," on a purin-free and creatin-free diet, found the elimination of creatinin and urea to be essentially normal, ammonia somewhat high, and as already mentioned, the uric acid distinctly increased. McKelvy and Rosenbloom came to the same conclusion. Their patient with congenital hemolytic jaundice also showed a normal excretion of urea, ammonia, amino-acids and creatinin, with a decided increase in uric acid elimination. These findings have been confirmed by Goldschmidt, Pepper and Pearce. The temporary change which occurred in the partition of creatinin and creatin, following the removal of the spleen in their patient will be referred to in the paragraphs on splenectomy.

Determinations of the partition of urea, ammonia, amino-acids, creatin and creatinin in *leukemia* have been carried out by many workers (Magnus-Levy(*c*), von Stejskal and Erben(*a*), von Jaksch(*j*), Halpern). The figures obtained are, on the whole, within the limits of normal physiological variation. Inasmuch as the details of these observations have already been presented in previous reviews of this subject, they will not be further discussed here.

Mineral Metabolism.—The paragraphs on mineral metabolism will be devoted to a consideration of the behavior of iron, phosphoric acid and the earthy metals and of sulphur. These substances have an especial interest in diseases of the blood because of the intimate relationship of iron to hemoglobin metabolism, and of phosphoric acid and sulphur to the catabolism of nucleoprotein and of body tissue protein, which, as has been pointed out, may at times be greatly accelerated in diseases affecting the blood and the blood-forming organs.

Iron Metabolism.—The importance of iron as a constituent of hemoglobin makes it a factor of great importance in the study of the anemias. But the progress which has been made in this phase of metabolism in disease has been limited to a large extent by the lack of accurate information concerning the assimilation and elimination of iron in health.

What knowledge we possess concerning the metabolism of iron has been concisely summarized by Pearce: "Iron is absorbed to only a very limited extent from the gastro-intestinal tract, so that when abundant in the food it passes from the intestine for the most part unchanged. As much as is absorbed is taken up chiefly from the small intestine and carried by the lymph, to be deposited in the liver and to a lesser extent in the spleen,

bone-marrow, and perhaps elsewhere, and this occurs whether the iron be in intimate organic combination, the so-called food iron, incapable of giving the characteristic microchemical reaction, or whether it be in the form of an organic or inorganic salt of iron (Pearce, Krumbhaar, and Frazier).

It has been shown by a number of workers (Morawitz(*b*)) that the amount of iron metabolized in the body so as to be eliminated in the excreta is only a small fraction of the iron ingested in the food or that derived from the disintegration of hemoglobin. The actual figures given by various workers (Lehmann(*b*), Stockman and Grieg, von Wendt) show some fluctuations. According to Sherman, the body in health eliminates only 7 or 8 milligrams of iron during the fasting state, and on a restricted diet from 5.5 to 12.6 milligrams per day, and the amount of food iron required for the maintenance of iron equilibrium in healthy men lies between 6 and 12 milligrams per day.

Other observers, however, give considerably higher values for total iron excretion. (Table 8.) Kennerknecht, for instance, in normal individuals found the fecal iron alone to average 25 milligrams per day. In the urine only small amounts of iron are eliminated in health. The quantities given by earlier workers vary from 1 to 8 milligrams. But at the present, since the work of Neumann and Mayer, about one milligram of iron for a period of twenty-four hours is considered the normal output.

It is obvious, therefore, that the organism must possess a great power of conserving its iron and of re-utilizing it through some form of intermediary metabolism. This phase of the process is little understood, save for the knowledge that the spleen and liver are the great depots for iron storage. The quantity of iron stored in the body and the extent to which the stored iron participates in metabolism are difficult to determine. For this reason what knowledge we possess concerning the utilization and elimination of iron both in health and in disease is for the most part based upon determinations of the balance between the amount of iron ingested and the amount excreted.

The influence of *hemorrhage* on the elimination and storage of iron has been investigated by some of the earlier workers (Morawitz(*b*)). These observations have emphasized certain points of difference between the metabolism of iron in the posthemorrhagic anemias and in those resulting from blood destruction. Following a loss of blood, the quantity of iron eliminated has been found to decrease; whereas, in the hemolytic anemias the urinary iron excretion usually increases. Furthermore, hemorrhage results in a lessened iron storage in the liver and spleen, while in the hemolytic anemias more than the normal quantity of iron is stored in these organs. Thus, William Hunter in a study of the intermediary iron metabolism in these two conditions noted an average of 19 milligrams of

TABLE 8

ELIMINATION OF IRON IN HEALTHY AND ANEMIC INDIVIDUALS

After Pearce, Krumbhaar, and Frazier: "The Spleen and Anemia."

J. B. Lippincott Co., 1918, page 236

Observer	Sex	Age	Iron in mgm.		Remarks
			Intake per Day	Output per Day	
Lehmann, Mueller, Munk, Zuntz	Male	26	Fasting	7.3 [5]	Professional fasters; 10 and 6 day periods respectively.
	Male	21	Fasting	7.7	
Stockman and Grieg	Male I	20	6.2 [1]	6.32 [4]	Healthy individuals.
			5.6	11.46 [2]	
	Male II	35	6.2	8.33	
	Female	23	3.5	3.73	
Von Wendt	Male 1	..	11.0 [1]	9.0 [4]	Nine periods of observation on two healthy individuals.
	2	..	6.0	11.0	
	3	..	10.0	14.0	
	4	..	8.0	9.0	
	5	..	17.0	42.0	
	6	..	7.0	15.0	
	7	..	19.0	24.0	
	8	..	28.0	34.0	
	9	..	27.0	32.0	
Sherman	Male	..	5.7 [3]	5.5 [4]	Three healthy individuals.
	Male	..	6.5	8.7	
	Male	..	7.1	12.6	
McKelvy and Rosenbloom	Female	11	8.8 [1]	32.51 [4]	Congenital hemolytic jaundice—5 day period.
Roth	Male	26	90.0 [3]	6.25 [4]	Hemolytic anemia. Splenectomized 3 years previously.
			150.0	4.32	
	Male	37	90.0	12.18	Splenectomized one month previously for trauma of spleen.
			200.0	33.07	
Bayer	Male	16	240.0 [1]	9.38 [5]	Two weeks after splenectomy for traumatic spleen rupture. Three months later.
			140.0	7.41	
			130.0	14.54	
			80.0	5.92	
			300.0	26.73	
	Male	16	240.0	8.40	Control: Fracture of tibia.
			140.0	7.29	
	Male	16	130.0	8.57	Control: Osteomyelitis; operation 14 days before.
			80.0	3.57	
			300.0	23.49	
	Female	19	130.0	13.86	Morbus Banti; 2¼ years after splenectomy.
	Female	25	130.0	10.20	Morbus Banti; ½ year after splenectomy.
	Female	27	60.0	21.46	Morbus Basedow; before thymectomy.
			60.0	32.70	Three weeks after.
			60.0	12.83	Six weeks after.
			60.0	19.00	Ten weeks after.
	Male	22	130.0	3.59	Morbus Banti; before splenectomy.
Goldschmidt, Pepper and Pearce	Male	5	3.77 [3]	8.29 [5]	Congenital hemolytic jaundice—Before splenectomy. 10 day period.
			4.56	4.11	After splenectomy, 10 day period.
Pepper and Austin	Male	40	16.5 [3]	17.0 [5]	Pernicious anemia. Before splenectomy, 5 day period.
			16.5	10.0	Two weeks after splenectomy, 4 day period.

[1] Iron intake determined by actual analysis.
[2] Two periods on same individual; bulk of feces in second period twice as great as in first.
[3] Iron intake estimated from tables.
[4] Urine and feces.
[5] Feces only.

iron in the liver and 23 milligrams in the spleen in three instances of posthemorrhagic anemia, as contrasted with 290 milligrams of iron in the liver, and 113 milligrams in the spleen in a case of hemolytic anemia. It has been suggested that the decreased elimination and the lessened iron storage noted after hemorrhage is probably due to the rapid utilization of iron for the rebuilding of the lost hemoglobin.

Studies of iron metabolism in *chlorosis* have been largely concerned with the factors of iron deficiency in the food and of faulty iron assimilation as possible causes of this disease, as well as with the efficacy and mode of action of organic and of inorganic salts of iron in the treatment of this condition.

The question raised by Bunge(*a*) concerning the absorption of inorganic iron in anemia and its value in chlorosis has been answered in the affirmative by most observers (E. Meyer(*c*)). According to the later work of Abderhalden(*c*) inorganic iron is beneficial in anemia not only because of its indirect stimulation of the blood-forming organs, but also because it is absorbed, assimilated and converted into hemoglobin precisely like food-iron. The elimination of iron in the urine and feces of chlorotic patients has been found variable. The results of different observers have been reviewed by Morawitz(*b*) and by Kennerknecht. Whereas some investigators give normal figures for urinary iron in chlorosis, others report a decreased or increased elimination. The large excretion of iron in the feces noted by von Hösslin(*b*) has been interpreted by him to mean that the anemia of chlorosis may be due to the excessive loss of iron through the intestine. Such a conception of the etiology of chlorosis is according to the critical analysis of Morawitz quite unlikely. He is inclined to the view that neither the faulty absorption nor the increased elimination of iron plays an important part in the causation of chlorosis. According to this observer further additions to our knowledge of the etiology of chlorosis will come not from the balance experiments thus far recorded, but rather from a better understanding of the intermediary iron metabolism in this disease.

The occurrence of excessive blood destruction in the *hemolytic anemias* gives the observations on iron elimination in these conditions particular significance. In the severe anemia produced experimentally by pyrodin, which gives rise to considerable breaking down of red cells, Samuely(*a*) noted an increased excretion of iron only in the feces; whereas patients with pernicious anemia with increased hemolysis may show a marked increase in the output of iron in the urine. In one patient three weeks before death, W. Hunter found as much as 32.26 milligrams of iron in the twenty-four-hour period of urine, and other observers (Hopkins, Jolles, Mayer(*a*)) report similar findings. The patients studied by Kennerknecht showed increased quantities of iron not only in the urine but also in the feces during certain periods of the disease. In their care-

ful metabolic study, however, Pepper and Austin(*c*) found a marked increase in the iron of the feces only after removal of the spleen.

Although an increased iron excretion in pernicious anemia may occur at times in the presence of greater blood destruction, it should be emphasized that the quantity of iron eliminated is no quantitative index of the amount of blood destroyed because unknown amounts of iron derived from the broken down hemoglobin are stored in the various organs and tissues of the body (Queckenstedt).

An excessive loss of iron from the body in hemolytic icterus has been a constant finding. Such a liberation of iron from broken-down hemoglobin would be expected in a disease in which hemolytic jaundice is combined with an increased fragility of the red blood-cells. In their patient, McKelvy and Rosenbloom found a marked increase in the excretion of urinary and fecal iron, the total loss for the five day metabolism experiment amounting to 0.1199 gram. Goldschmidt, Pepper, and Pearce, who limited their determinations to the fecal iron, also report a large loss of iron before splenectomy, followed by a decrease of 40 per cent after operation. This large output of iron in the period before splenectomy is due, according to these observers, to the increased quantities of iron freed in the body consequent to the excessive destruction of red cells. The decreased elimination after splenectomy is probably the result of a cutting off of this loss with a return to a nearly normal balance between intake and output.

More difficult to explain is the increased excretion of iron observed in certain instances of *leukemia* (Hoffmann, Kennerknecht). The patients studied by Kennerknecht had had shorter or longer exposures to the röntgen-rays. In two of the cases in which the leukocyte counts changed very slightly, following radiation, the total iron output was found to be 36.68 and 22.96 milligrams. The urinary iron in these instances amounted to 1.55 and 7.21 milligrams respectively. The large output of iron in the urine in the latter patient cannot be explained by the greater leukocyte destruction, since the counts were only slightly reduced by the action of the rays. It appears not unlikely, according to Kennerknecht, that the increased elimination noted in these patients as well as in the untreated ones is the result of a diminished iron storage by a diseased spleen.

In the third patient in whom röntgen-ray exposures caused a drop in the white cell count from 90,000 to 44,000, the output of iron reached 68.61 milligrams per day. That this high iron elimination is not entirely the result of the destruction of leukocytes follows from the study of the other patients. More plausible is the explanation that it is the result of a concomitant breaking down of erythrocytes which not infrequently follows exposure to the röntgen-rays.

Metabolism of Phosphoric Acid, Calcium, and Magnesium.—The

metabolism of phosphoric acid is intimately connected with that of the earthy metals, calcium and magnesium, on the one hand, and with the excretion of nitrogenous substances, especially of uric acid, on the other. A critical summary of the normal and pathological metabolism of these substances has been given by Magnus-Levy(*h*) and by Morawitz(*b*).

This phase of mineral metabolism in blood diseases has been reviewed by Strauss(*e*). In the posthemorrhagic anemias, the elimination of phosphoric acid has been found variable. Jacob and Bergell in a case of posthemorrhagic anemia found a retention of phosphoric acid, whereas Strauss reports only a slight change following the removal of a small quantity of blood. After an acute hemorrhage in dogs Gies noted a variable effect on the excretion of phosphorous compounds, mainly a slight decrease. This tendency to the retention of phosphorus has been attributed by him to the stimulated nuclear anabolism and to the increased nucleoprotein formation following the loss of blood.

Chlorotic patients also show great variability in the excretion of phosphoric acid and the earthy metals. Little has been added to our knowledge of this subject since the earlier observations of Vannini. Of the five patients studied by this worker some manifested a tendency to the retention and others toward the increased excretion of these substances. The majority of the patients eliminated more calcium and magnesium in the feces than in the urine.

Patients with *pernicious anemia* have been found to show wide fluctuations in the elimination of phosphoric acid, calcium, and magnesium during different periods of the disease. Among the earlier observers some report a marked loss of phosphoric acid (Schmidt, R.), others a retention (von Moraczewski(*d*), Strauss(*e*)), and still others (von Stejskal(*b*)) an equilibrium between the amount absorbed and the quantity excreted. Of great interest is the considerable increase in the total phosphates which Denis(*d*) reports in two patients with pernicious anemia following splenectomy.

As a rule, the quantity of calcium lost was found to exceed the gain (Schmidt, R., von Moraczewski(*d*)); whereas, the absorption and excretion of magnesium oxid were more frequently in equilibrium. Both earthy metals, however, may be excreted in excessive amounts in other types of severe anemia. Thus in a five-day metabolism experiment on a patient with congenital hemolytic jaundice, McKelvy and Rosenbloom noted a loss of calcium and magnesium oxids, amounting to 0.482 gram of the former and 0.924 gram of the latter. This patient showed a tendency to retain phosphorus.

The great increase in the breaking down of nucleoprotein which occurs in certain forms of leukemia is associated with the appearance in the urine not only of increased quantities of uric acid and purin bases but also of phosphoric acid. In acute leukemia, in particular, has the excretion of

phosphoric acid been found excessive. The figures obtained by Magnus-Levy(*c*) are exceedingly remarkable. One of his patients with acute leukemia showed a loss of about 15 grams of phosphorus pentoxid in fifteen hours. The loss of phosphorus, while decided, was not so remarkable as the loss of nitrogen. Similar, though less striking, losses have been observed by others. Edsall's(*b*) patient, for instance, on a diet containing 7.25 grams of nitrogen, and 1.84 grams of phosphorus eliminated in the urine 29.534 grams of nitrogen and 3.056 grams of phosphorus pentoxid. The loss of phosphorus in the urine and feces of this patient was probably over 2 grams.

In the chronic forms of leukemia the excretion of phosphorus fluctuates somewhat, as does the elimination of nitrogen, with the rapid changes in the pathological processes which underlie this disease. Thus von Moraczewski(*c*), and Musser and Edsall found a retention of phosphoric acid in myelogenous leukemia, whereas von Stejskal and Erben(*a*) noted a slight increase in this form of the disease and a moderate retention in a patient with lymphatic leukemia.

It appears, on the whole, that the abnormally high values for phosphoric acid excretion were observed usually only in severe cases, and for the most part towards the end of life. The retention of phosphates noted in certain instances of leukemia has been attributed to the rapid building of leukemic tissue, a tissue especially rich in phosphorus.

Calcium and magnesium excretion in leukemia and the ratio which phosphoric acid bears to these has been studied especially in connection with the question of the source of the increased quantities of phosphoric acid. Considerable variability of results is to be found in the literature. Sometimes a retention, at other times an increased excretion, and at still other times equilibrium between the intake and output have been reported. Those who have found the excretion of calcium and magnesium considerably greater than the excretion of phosphoric acid have been inclined to the view that the increased quantities of phosphoric acid eliminated arise from the disintegration of osseous tissue. Calculations, however, of the ratio between the nitrogen and uric acid eliminated and the phosphorus excreted point rather to the conclusion that the increased output of phosphoric acid, in those conditions in which it occurs, is to be referred to the decomposition of nitrogenous substances, especially those containing the nuclein radical.

Sulphur Metabolism.—It is well known that the excretion of sulphur, and more especially of neutral sulphur, runs more or less parallel with the intensity of protein metabolism, so that, in a sense, a knowledge of the quantity of sulphur excreted serves as a check on the elimination of nitrogenous substances. Whereas, in some instances of anemia and leukemia, the excretion of sulphur has been found to parallel the output of nitrogen, this finding has not been constant.

In experimental posthemorrhagic anemia, Gies found a definite rise in the total urinary sulphur, which corresponded well with the increased protein catabolism. Wide fluctuations in the elimination of sulphur have been noted in chlorosis. For neutral sulphur, Schmidt's values range from 13 to 23 per cent and Vannini's from 13 to 26 per cent of the total sulphur. The results of the latter observer indicate, on the whole, the existence of some parallelism between sulphur elimination and nitrogen excretion.

The figures for the excretion of ethereal sulphates in chlorosis have been found relatively low by most workers (von Noorden, Vannini). This is of interest in connection with the view of some observers concerning the presence of excessive intestinal putrefaction in chlorotic patients.

Sulphur metabolism in the hemolytic anemias has been little studied, especially by recent workers. From the available contributions, it is apparent that great fluctuations in the elimination of sulphur compounds may exist in these conditions. In severe forms of anchylostomiasis anemia, Schupfer and De Rossi(*a*) noted high values for neutral sulphur, in some instances amounting to twice the normal figure. The results, however, obtained in patients with primary pernicious anemia have been quite variable. Thus both of the patients studied by Schmidt showed an increased output of neutral sulphur and a normal or relatively low excretion of ethereal sulphates. Von Moraczewski, on the contrary, obtained practically normal figures for neutral sulphur and strikingly low outputs of ethereal sulphates in his carefully studied pernicious anemia patients. Similar results have been found by Denis(*d*), who further demonstrated that splenectomy produces no appreciable change in the excretion of sulphur.

Concerning sulphur metabolism in congenital hemolytic icterus, only a few observations exist in the literature. So far as can be determined, the complete metabolic study of McKelvy and Rosenbloom give the only valuable data for sulphur metabolism in this disease. Their patient lost 1.88 grams of sulphur in a period of five days, a loss which paralleled somewhat the increased elimination of nitrogen. And except for the marked increase in the excretion of ethereal sulphates on the first and last days of the metabolism experiment, which they attributed to intestinal putrefaction, the partition of urinary sulphur was found normal.

The observations on the excretion of sulphur compounds in leukemia are also few in number. From the available studies, it appears on the whole that the total quantity of sulphur present in the urine of leukemia patients is approximately proportional to the amount of nitrogen excreted (von Moraczewski(*c*), Taylor(*b*)(A. E.), von Stejskal and Erben(*a*)).

Chemical Changes in the Nitrogenous Metabolites and Fats of the Blood.—Up to the present time comparatively little application has

been made of the more recent chemical methods of blood analysis to the study of the level of the nitrogenous and other metabolites in the blood of patients suffering from anemia and leukemia. The few observations which have been recorded are of great interest because of the possible light which they may throw upon the problems of protein metabolism from the standpoint of blood and tissue analysis as well as upon the influence of splenic function on the fat and lipoid content of the blood.

The latter problem, as was pointed out, is closely linked with the influence of cholesterol and the unsaturated fatty acids in changing the conditions of hemolysis after splenectomy.

The level of the nitrogenous constituents of the blood in anemic and in leukemic states has been determined by only a very few observers. Following hemorrhage in animals, Taylor and Lewis, and Buell(*a*) noted a rise in the non-protein nitrogen of the blood. The excessive tissue proteolysis to which hemorrhage may give rise has already been commented upon; and it is to this factor that these observers are inclined to attribute the increase of this fraction in the blood in acute posthemorrhagic conditions, the breaking down of body protein being, in a measure, compensatory so as to bring about a replacement of the lost circulating protein.

In her studies on the influence of splenectomy on metabolism in anemia, Denis(*d*) records observations on the non-protein nitrogen of two patients with pernicious anemia and on one with "family jaundice." All of these showed practically normal values for this fraction both before and after splenectomy. In leukemia, however, Martin and Denis found a high non-protein nitrogen in the blood.

Of the other components, urea and amino nitrogen were also found to be increased in acute posthemorrhagic anemia, and uric acid markedly so in leukemia (Folin and Denis(*d*)).

The studies of Eppinger and of King on the *blood fat* of normal and splenectomized animals has already been referred to in the paragraphs on the regulatory function of the spleen in blood formation and destruction. These workers, it was pointed out, found after removal of the spleen, an increase in the total fats and cholesterol of the blood, and a decrease in the unsaturated fatty acids, findings which, on the whole, have not been confirmed by other observers. Thus Dubin and Pearce found the total fats and the unsaturated fatty acids practically the same both before and after removal of the spleen, an observation which agrees with that of Denis(*d*), who noted no change in the total fatty acids of the blood in different forms of anemia.

Determinations of the cholesterol content of the blood possess especial interest in experimental and clinical anemias characterized by hemolysis. A decreased blood cholesterol has been found by Dubin in experimental trypanosome anemia and by Bloor(*b*), Denis(*d*) and Gorham

and Myers in pernicious anemia. The practical significance of this observation is apparent when it is recalled that cholesterol has an antihemolytic action and that it may increase noticeably in the blood consequent upon improvement in the blood picture, whether this result from a spontaneous remission or whether it be brought about by transfusion or splenectomy.

The Influence on Metabolism of Some Measures Used in the Treatment of Diseases of the Blood

Diet.—The employment of forced feeding and more particularly of high protein diets in pernicious anemia and allied conditions is of great interest in view of the doubt which still exists as to whether or not it is possible to effect an assimilation of protein in anemic states. The problem is closely linked with the question of increased protein destruction in anemia and leukemia, a discussion of which was taken up in the paragraphs on protein metabolism.

Whereas some investigators have experienced difficulty in obtaining a nitrogen balance in certain anemic conditions (von Stejskal(*a*), Rosenqvist, Umber(*b*), Minot(*a*), McKelvey and Rosenbloom), there appears to be little doubt that even the most severe anemias may run their course without injury to the body protein, and without any appreciable disturbance in the nitrogenous metabolism. It has been possible not only to maintain some patients with pernicious anemia in nitrogen equilibrium on approximately the same small quantity of protein as would be required in health (Bernert), but also to obtain a retention of nitrogen in these patients to a greater or lesser extent (Goldschmidt, Pepper and Austin(*c*), Mosenthal(*d*), Peppard).

Mosenthal(*d*), in particular, has succeeded in obtaining markedly positive nitrogen balances in three patients with pernicious anemia and in one patient with chronic myelogenous leukemia, complicated by secondary anemia. These patients received from 50 to 60 calories per kilogram per day and showed on this intake an average nitrogen retention of from 3 to 6 grams daily. Similar results have been obtained recently by Peppard, who recommends a dietary yielding from 60 to 65 calories per kilogram per day, this to be given in proportions of protein 16 per cent, fat 42 per cent, and carbohydrate 42 per cent.

Transfusion.—Thus far only a limited number of observations have been carried out on the influence of transfusion upon gaseous and nitrogenous metabolism. Delchef and Hári(*b*) have reported the only metabolism studies on true transfusion in experimental anemias. Immediately after the anemic animal received the injected blood Delchef found the oxygen consumption greatly elevated. Similarly, Hári found the metabolism somewhat increased on the injection of fresh blood into normal

animals. The heightened metabolism noted by both observers has been attributed to the agitation and dyspnea attendant on the operation rather than to the direct effects of transfusion itself.

Tompkins, Brittingham, and Drinker, on the contrary, found that transfusion in clinical cases of anemia, and more especially in pernicious anemia, usually lowers the basal metabolism, which may reach a normal or a diminished level depending upon the rate before transfusion. The factors underlying this fall in the metabolic rate are not well understood. Those who are inclined to attribute the heightened metabolism so frequently observed in anemia to the increased muscular work required by the more rapid respiration and heart rate, maintain that transfusion lowers the calorific output by diminishing the pulse and respiratory activity. That restraint of the muscular compensations, however, is not the only cause of the lowered metabolism follows from the experiments of Drinker and his associates. They found, for instance, that, although transfusion produces an almost immediate check to the accelerated heart and lung action, the maximum effect on the metabolism takes place only after several days. Such an observation would seem to suggest that transfusion produces its effect not alone by influencing the compensatory muscular activity but also by modifying, in some way, certain other factors which exert an influence on the metabolism of the anemic individual.

The influence of transfusion on the nitrogenous metabolism has been studied experimentally by Haskins(*a*) and in man by Crile(*a*). In two experiments on dogs, extending over an average period of two days before and two days after operation, Haskins observed that transfusion following hemorrhage produced a greater rise in the percentage output of total nitrogen, ammonia nitrogen, uric acid and creatinin than a moderate hemorrhage alone. A comparison of the figures obtained in one of the animals after a moderate hemorrhage followed by a transfusion of approximately the same quantity of blood is of interest: the total nitrogen, ammonia nitrogen, and uric acid increased 14.7 per cent, 11 per cent and 14 per cent respectively after hemorrhage as compared with 20 per cent, 15 per cent, and 18 per cent respectively after transfusion. The creatinin, however, decreased 7.8 per cent after hemorrhage, but increased 3.7 per cent after transfusion; whereas the percentage of urea nitrogen fell in both instances, but slightly more so after hemorrhage alone.

A similar rise in the excretion of nitrogen, and ammonia after transfusion has been observed clinically by Crile in one patient. In this instance, the nitrogen after transfusion rose from 10.3 grams to 16.5 grams in the twenty-four-hour period, and the ammonia increased from 0.16 gram to 0.47 gram. Both of these constituents returned to practically the original level by the fifth day after the transfusion.

Splenectomy.—The use of splenectomy as a mode of treatment in diseases of the blood is now limited for the most part to the so-called primary anemias, to Banti's disease, and to hemolytic icterus. In considering therefore the influence of splenectomy on metabolism, attention will be directed only to these conditions.

Experimental Observations.—The effect of removing the spleen in normal animals on the elimination more especially of nitrogen and iron is of great interest because of the possible relationship existing between the quantity of these substances excreted and the repair of the anemia which is known to follow splenectomy. Some of the earlier work on normal animals is reviewed by Pearce and his co-workers. Careful control of the nitrogen intake and the long periods of observation give to the experiments of Pearce and his associates greater value than is possessed by the work prior to theirs.

The nitrogen metabolism after splenectomy was followed in four animals for periods varying from three days to three months. In one of these a positive nitrogen balance of 0.45 gram before operation remained practically unchanged three days after splenectomy. Essentially the same results were obtained in a second animal eight weeks after operation, while in two other instances a moderate retention of nitrogen occurred; a positive balance of 0.48 gram per day in one of these experiments became slightly negative ten days after splenectomy, and definitely positive again three months after operation when the animal was retaining 1.10 grams of nitrogen daily. Such experimental evidence does not support the view that the spleen markedly influences nitrogen metabolism. The moderate retention of nitrogen noted during certain periods after splenectomy is probably due to the utilization of nitrogen for the repair of the anemia which usually follows removal of the spleen.

Whether the spleen plays any essential part in iron metabolism is a question raised by the work of Grossenbacher and of Zimmermann. They studied the iron elimination of four puppies with and without splenectomy, and found that there was a marked increase in the output of iron following removal of the spleen, an increase which persisted at times for ten months. From these experiments, they concluded that the spleen is an important organ in intermediary metabolism, enabling the body to conserve and reutilize its iron.

This view, however, is not supported by the careful experiments of Pearce and his associates. Austin and Pearce studied the metabolism of iron in dogs both before and from four days to twenty months after splenectomy. Only three out of the five animals showed an increased iron elimination after operation, and then only during the first two weeks, this being absent one month, nine months, and twenty months after splenectomy. In a later series of experiments, Goldschmidt and Pearce noted in one out of four splenectomized dogs an increased elimina-

tion of iron amounting to 21.6 per cent ten days after operation and to 148 per cent three months later. As this animal was the only one to show any unusual elimination of iron after splenectomy, they are inclined to attribute the rise in iron excretion to the anemia, rather than to the absence of the spleen.

Nor has any gross abnormality been made out in the utilization of fat by splenectomized animals. The experiments of Pearce and his coworkers in this connection are unique in the literature and are of interest in view of the fact that splenic function has been thought to influence in some way the metabolism of fat.

Clinical Observations.—Whereas the results of metabolism experiments on splenectomized animals are essentially negative, definite changes have been observed after the removal of the chronically diseased spleen in man. The reason for this difference is not far to seek. Splenectomy in man is done usually in the presence of an anemia of more or less severity, which may account in large measure for the changes noted. Furthermore, the reversion to more or less normal conditions after splenectomy is to be regarded as the result of the removal, not of a normal function of the spleen, but rather of an altered function which expresses itself in a hemolytic or toxic activity.

Metabolic studies made before and after the removal of the diseased spleen in man are few in number. The only available contributions are those of Umber(*b*), Minot(*a*), Goldschmidt, Pepper, and Pearce, Pepper and Austin(*c*), and Denis(*d*).

In Banti's disease, Umber found it easier to obtain nitrogen equilibrium after splenectomy, a fact which he attributes to the pathologic destruction of protein resulting from the toxic action of the diseased spleen. Denis, on the contrary, found the nitrogen elimination practically unchanged in a patient with Banti's disease and in one with "atypical splenic anemia." The uric acid elimination was diminished in the first patient and increased in the second.

Metabolism studies following splenectomy in patients with pernicious anemia have likewise yielded discordant results. In Minot's patient, removal of the spleen converted a slightly negative into a slightly positive balance and caused an increase in the percentage of urea nitrogen. On the other hand, the nitrogen balance in Pepper and Austin's patient was slightly positive before operation. Splenectomy in this instance caused an increased retention of nitrogen fourteen days after removal of the spleen; the balance returning to the pre-operative level one month later. An observation of interest in this patient was the elimination of uric acid which showed a decrease after splenectomy of 22 per cent from the normal figure of the pre-operative period (Table 6). Denis, however, could not substantiate this finding. In neither one of her two pernicious anemia patients did she observe any constant effects on the total nitrogen

TABLE 6

EFFECT OF SPLENECTOMY ON ELIMINATION OF URIC ACID, IRON AND UROBILIN IN PERNICIOUS ANEMIA

Period	Date	Weight Pounds	Nitrogen Intake Grams	Urine			Feces		Total Nitrogen Output Grams	Nitrogen Balance gm.	Urobilin and Urobilinogen.
				Amount c.c.	Total N Grams	Uric Acid mg.	Total N Grams	Iron mg.			
I	4/28/15	170¾	16.7	1,550	14.8	762	1.46	17	16.26	+ 0.44	4/9/15 to 4/12/15, 18,300 per day.
	4/29/15	.....	17.6	1,820	16.2	824	1.46	17	17.66	— 0.06	
	4/30/15	.....	16.7	1,600	13.7	728	1.46	17	15.16	+ 1.54	
	5/ 1/15	.....	17.2	1,680	14.5	788	1.46	17	15.96	+ 1.24	
	5/ 2/15	172½	16.6	2,200	16.2	852	1.46	17	17.66	+ 1.06	
	Average	.....	16.96	1,770	15.08	791	1.46	17	16.54	+ 0.42	
	6/12/15	175	Splenectomy								
II	6/24/15	.....	15.70	1,160	10.86	500	1.09	10	11.95	+ 3.75	6/25/15, 16,500 per day.
	6/25/15	.....	16.80	1,340	12.48	520	1.09	10	13.57	+ 3.23	6/28/15 to 7/2/15, 16,000 per day.
	6/26/15	.....	17.00	1,600	14.76	740	1.09	10	15.85	+ 1.15	
	6/27/15	.....	17.30	1,590	15.54	680	1.09	10	16.63	+ 0.67	
	Average	.....	16.70	1,420	13.41	610	1.09	10	14.50	+ 2.20	
III	7/ 6/15	160½	17.20	1,600	14.20	680	1.97	..	16.17	+ 1.03	
	7/ 7/15	.....	16.30	1,380	14.10	680	1.97	..	16.07	+ 0.23	
	7/ 8/15	.....	16.60	.....	.....	...	1.97	..	.....	.....	
	7/ 9/15	.....	17.20	1,210	13.44	500	1.97	..	15.41	+ 1.79	
	7/10/15	.....	16.80	1,310	15.06	620	1.97	..	17.03	— 0.23	
	7/11/15	162	16.40	1,290	14.82	640	1.97	..	16.79	— 0.39	
	Average	.....	16.75	1,360	14.32	624	1.97	..	16.29	+ 0.46	
	8/22/15	190	.....	.....	.....	...	....	..	.....	.....	8/18/15 to 8/22/15, 2,300 per day.

After Pearce, Krumbhaar, and Frazier: "The Spleen and Anæmia." J. B. Lippincott Co., 1918, page 222.

excretion after operation. The ammonia output, however, was increased in one patient and the uric acid in another during the post-splenectomy period.

Definite changes in the nitrogen metabolism and in the partition of certain of the nitrogenous constituents of the urine have been noted to follow removal of the spleen in hemolytic jaundice. After splenectomy in their patient, Goldschmidt, Pepper and Pearce observed a tendency toward nitrogen retention, a decrease in the elimination of uric acid to the extent of 47 per cent of the preoperative level, and an increase in the quantity of creatin at the expense of the creatinin.

Whether the changes noted in the post-splenectomy period in pernicious anemia and in hemolytic jaundice are the result of the improvement of the anemia or due to the removal of a perverted splenic function, it is difficult to determine. Before this question can be satisfactorily answered, it will be necessary to carry out more observations before and after splenectomy on the metabolism of essentially normal individuals or of those with simple lesions of the spleen attended by the development of an anemia.

The determinations of iron elimination before and after splenectomy in man are few in number (Table 8). Bayer(*a*)(*b*) and also Roth report an increased output of iron following the removal of a normal spleen for rupture of this organ. Since no determinations were made before operation, it is difficult to interpret these results, more particularly as wide variations in the iron figures are known to exist in normal individuals.

Thus far, the patients studied by Pearce and his co-workers are the only recorded instances in which careful observations were made on the iron elimination before and after removal of the spleen in blood diseases involving this organ. In the patient with pernicious anemia, the iron output, although never above normal, showed a decrease of 40 per cent after operation. A similar decrease was noted after splenectomy in a patient with congenital hemolytic icterus. In this instance, there was a great loss of iron in the pre-splenectomy period, which it is most plausible to assume was the result of excessive blood destruction produced by a toxic factor in the diseased spleen, the removal of which effected a restoration of the iron balance to a more normal state.

Observations on the metabolism of fats are limited to two patients with hemolytic icterus (McKelvy and Rosenbloom, Tileston and Griffin). Examination of the feces of these patients both before and after splenectomy failed to establish the existence of any definite influence of the pathological spleen on the utilization of fat, the results in these respects coinciding with those found in normal animals.

In summary, it seems justifiable to conclude from the available evidence that removal of the spleen in the hemolytic anemias is, as a rule,

TABLE 7

METABOLISM IN CONGENITAL HEMOLYTIC ICTERUS BEFORE AND AFTER SPLENECTOMY

Period	Date	Weight in Kg.	Nitrogen Intake gm.	Urine										Feces; Total Nitrogen gm.	Total Nitrogen Output gm.	Nitrogen Balance gm.	Clinical Notes and Temperature
				Amt. c.c.	Specific Gravity	Hydrogen Ion Conc.*	Total Nitrogen gm.	Urea gm.	Ammonia gm.	Uric Acid gm.	Total** Creatinin gm.	Creatinin gm.	Creatin gm.				
I	12/ 4/14	17.7	6.45	480	1.022	6.15	6.09	5.25	0.36	0.468	0.476	0.289	0.217	0.54	6.63	— 0.18	98.2
	12/ 5/14	....	9.00	530	1.018	5.70	5.46	4.53	0.33	0.468	0.398	0.235	0.154	0.54	6.00	+ 3.00	98.4
	12/ 6/14	....	5.16	480	1.020	5.50	4.99	4.18	0.32	0.468	0.309	0.226	0.096	0.54	5.53	— 0.37	101.4
	12/ 7/14	....	5.66	400	1.025	5.85	6.38	5.54	0.26	0.516	0.385	0.270	0.133	0.54	6.92	— 1.26	99.6
	12/ 8/14	....	6.47	550	1.019	6.15	6.54	5.60	0.32	0.490	0.405	0.261	0.167	0.54	7.08	— 0.61	100.2
	Average	....	6.55	488	21	5.87	5.89	5.02	0.32	0.482	0.389	0.256	0.153	0.54	6.34	+ 0.12	.....
II	12/ 9/14	....	4.91	280	1.030	6.15	3.96	3.41	0.19	0.410	0.271	0.191	0.093	0.52	4.48	+ 0.43	99.6
	12/10/14	....	6.12	500	1.020	6.30	5.18	4.40	0.31	0.544	0.369	0.289	0.093	0.52	5.70	+ 0.42	100.4
	12/11/14	....	4.12	270	1.028	6.15	3.00	2.75	0.15	0.544	0.211	0.191	0.023	0.52	3.52	+ 0.60	99.8
	12/12/14	....	5.03	320	1.026	6.00	4.07	3.43	0.20	0.460	0.271	0.241	0.035	0.52	4.59	+ 0.44	100.2
	12/13/14	18.2	4.90	360	1.027	6.00	4.98	4.20	0.24	0.788	0.320	0.270	0.058	0.52	5.50	— 0.60	98.4
	Average	....	5.02	346	26	6.12	4.24	3.64	0.22	0.549	0.288	0.236	0.060	0.52	4.76	+ 0.26	.....
III	1/20/15	....	....	440	1.019	....	4.59	....	....	0.400	0.279	0.225	0.063				
	1/21/15	....	....	410	1.029	....	4.29	....	....	0.560	0.270	0.209	0.071				
	1/22/15	....	....	415	1.033	....	3.51	....	....	0.520	0.259	0.207	0.060				
	1/23/15	....	....	690	1.019	....	3.81	....	....	0.460	0.245	0.215	0.035				
	1/24/15	....	....	500	1.024	....	4.31	....	....	0.614	0.300	0.270	0.035				
	Average	....	....	491	25	....	4.10	....	....	0.511	0.271	0.225	0.053				
	1/28/15		Splenectomy														
IV	2/ 6/15	18.2	7.08	540	1.023	6.00	5.61	4.95	0.22	0.326	0.300	0.203	0.113	0.35	5.96	+ 1.12	99.6
	2/ 7/15	....	6.23	590	1.020	6.00	4.71	4.08	0.21	0.294	0.283	0.180	0.119	0.35	5.06	+ 1.17	99.0
	2/ 8/15	....	6.41	570	1.020	6.00	4.80	4.16	0.19	0.294	0.311	0.197	0.132	0.35	5.15	+ 1.26	99.8
	2/ 9/15	....	4.97	570	1.020	6.70	3.63	3.11	0.12	0.290	0.234	0.176	0.109	0.35	3.98	+ 0.99	Bronchitis 103.2
	2/10/15	....	4.99	450	1.023	6.80	3.06	2.68	0.10	0.226	0.194	0.176	0.063	0.35	3.41	+ 1.58	102.2
	Average	....	5.94	544	21	6.30	4.36	3.80	0.17	0.286	0.264	0.172	0.107	0.35	4.71	+ 1.22	.....
V	2/11/15	....	6.20	630	1.020	5.70	6.15	5.37	0.31	0.296	0.337	0.287	0.058	0.40	6.55	— 0.35	99.4
	2/12/15	....	5.27	350	1.024	5.50	4.83	4.34	0.23	0.272	0.288	0.203	0.041	0.40	5.23	+ 0.04	98.8
	2/13/15	....	4.83	530	1.022	6.00	5.64	4.83	0.31	0.320	0.290	0.253	0.043	0.40	6.04	— 1.21	99.0
	2/14/15	....	5.38	360	1.032	6.80	4.08	3.54	0.14	0.224	0.238	0.195	0.050	0.40	4.48	+ 0.90	Otitis media 99.0
	2/15/15	....	6.17	430	1.025	6.70	4.73	4.13	0.18	0.218	0.248	0.203	0.052	0.40	5.13	+ 1.04	99.0
	Average	....	5.57	460	25	6.14	5.09	4.44	0.23	0.266	0.272	0.228	0.049	0.40	5.49	+ 0.08	.....

After Pearce, Krumbhaar, and Frazier: "The Spleen and Anæmia." J. B. Lippincott Co., 1918, page 212.

* Expressed as negative logarithms.
** Includes preformed creatinin and creatin as creatinin.

followed by a reduction in the elimination of uric acid, iron, and urobilin, changes which point to diminished blood destruction.

Röntgen-Rays and Radium.- It is now generally accepted that the röntgen-rays and radium are practically identical in their effect upon the tissues and the biochemical processes of the body. As a result of the careful histological studies of Heinecke, Warthin(*a*), and Proescher and Almquest, as well as those of a number of other observers, it has been established that both forms of radiant energy exert a destructive action on the entire hemopoietic system, and more especially upon the lymphatic tissues and the bone-marrow. All of the white blood-cells, both in the circulation and in the blood-forming organs, are attacked, the effect being, however, particularly selective for the cells of the lymphocytic series (Taylor, Witherbee and Murphy). And so far as the röntgen-rays are concerned, it has been found that their action is essentially the same in patients suffering from leukemia as in normal individuals (Aubertin, Warthin(*b*)).

The effects produced by radiation upon the metabolic processes of normal animals and of patients, treated for disorders other than those of the blood, are in many respects similar, although not so striking, to those noted in leukemia. Animals exposed for shorter or longer periods to the action of the röntgen-rays show, in most instances, an increased elimination of total nitrogen, uric acid, purin bases, and phosphorus (Quadrone, Benjamin and von Reuss, Lommel(*b*)). The level of urinary nitrogen in such animals may at times rise to from 50 to 100 per cent above the normal base line, this rise being accompanied by a high non-protein nitrogen of the blood, which may increase to twice or three times the normal on the day before death (Hall).

Many observers have called attention to the fact that the röntgen-rays and radium are capable also of producing changes in the metabolism of individuals, suffering from affections other than blood diseases. Thus Edsall and his associates have demonstrated that a great destruction of tissue may follow exposure to the röntgen-rays in certain nutritional disorders, and Bloch, who studied the metabolism of a patient treated for chronic eczema, noted that the rays caused an increase in the output of uric acid, purin bases and phosphorus pentoxid in the urine. Similar results were obtained by Linser and Sick on five patients under röntgen treatment for various skin diseases. All of these patients showed, besides the increase in the total urinary nitrogen, to which attention had been previously directed by Baermann and Linser, also a marked rise in the output of uric acid and purin bases. Analogous changes in metabolism following the use of radium have been described by Kikkoji, who found a significant rise in the basal metabolism, as well as an increased elimination of total nitrogen and uric acid in a normal individual and in one suffering from chronic arthritis. Far more striking, however, are

the evidences of tissue destruction produced by both forms of radiant energy in the leukemias, in which conditions the influence of radiation upon metabolism has been more extensively studied.

The effect produced by the röntgen-rays on the basal metabolism in leukemia was studied in Grafe's patient, T. S. (Table 4). In this instance, the heat production per square meter per hour, which was 68 calories before treatment, fell to 52 calories and later to 48 calories while under treatment. During this period, the leukocytes fell from

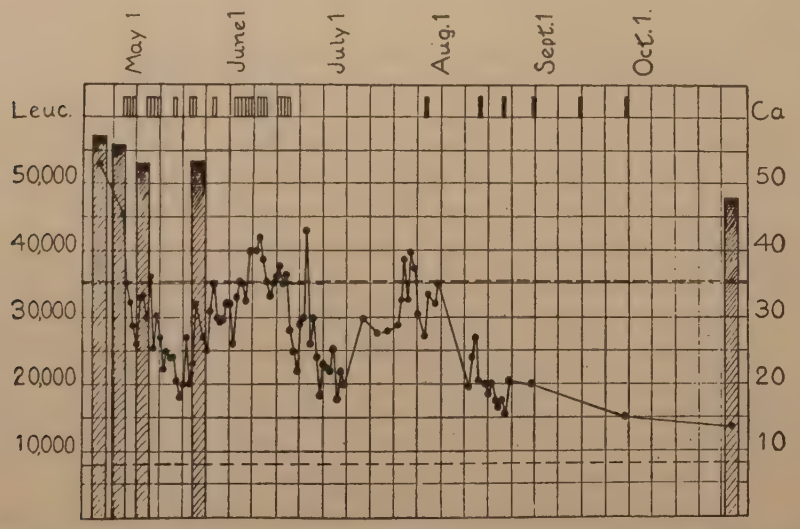

Fig. 4.—Chart showing the effect of röntgen ray and radium therapy on the basal metabolism of a patient with lymphatic leukemia. Basal metabolism, shaded columns, and the leukocytic count, black dots and lines. The hollow rectangles at the top indicate röntgen treatments, and the black ones radium treatments. The perpendicular rulings indicate periods of one week. The upper broken line represents the average basal metabolism for men from 50 to 60 years of age; the lower, the normal leukocyte count. (After Murphy, J. B., Means, J. H., and Aub, J. C. Arch. Int. Med., 1917, xix, 905.)

820,000 to 200,000. Murphy, Means and Aub, on the other hand, observed no appreciable action of the rays on the basal metabolism of a patient with chronic lymphatic leukemia, whereas radium treatment produced striking results. The leukocyte curve showed a more constant fall and the basal metabolic rate fell to 47.7 calories per square meter per hour, a calorific output only 36 per cent above the normal average for men of the patient's age as compared with 44 per cent, the figure obtained before treatment (Fig. 3). A similar drop in the basal metabolism following the use of radium in an instance of myelogenous leukemia was found by Edsall and his associates.

The nitrogenous and phosphoric acid metabolism after röntgen-ray and radium treatment has been studied by many observers. In a patient

with myelogenous leukemia treated by the röntgen-rays Lossen and Morawitz found a diminished excretion of total nitrogen, uric acid, and phosphorus pentoxid. On continued treatment, the uric acid content decreased, the nitrogen elimination remained the same and the phosphorus content increased. With the exception of Cavina, who noted no increase either in the total nitrogen or uric acid excretion of a patient with lymphatic leukemia under röntgen-ray treatment, the majority of workers (Heile(*b*) and Musser and Edsall) have been able to confirm the findings of Lossen and Morawitz.

In view of the greater cellular destruction which occurs under radiation, the behavior of the uric acid is of particular interest. Although in some instances of leukemia, the uric acid output was found to be high during treatment, and to fall coincidently with the leukocyte count, this was not the case in other patients in whom the uric acid elimination continued high even in the presence of a leukopenia. This absence of parallelism between the quantity of uric acid excreted and the degree of leukocytic disintegration has also been observed by other workers (Mohr(*i*)).

The findings of Musser and Edsall are especially interesting in this connection. These observers noted that where the röntgen-rays have no beneficial effect clinically, they also have little effect on the nitrogenous metabolism; whereas evidences of clinical improvement went hand in hand with a considerable increase in the elimination of nitrogen, uric acid, purin bases, and phosphorus pentoxid. In one patient the rise in the excretion of these substances expressed in the form of percentage of the amount previously eliminated was in round numbers: nitrogen about 70 per cent, uric acid about 60 per cent, purin bases about 260 per cent, and phosphates about 200 per cent. This striking phosphorus excretion after röntgen-ray exposure is all the more remarkable because of the retention of phosphorus which has been noted by these observers during certain periods of the development of the leukemic process, a retention which they attribute to the constant construction of tissues that are rich in phosphorus.

As yet, little is known concerning the chemical changes brought about in the blood of patients with leukemia treated by the röntgen-rays. In a very recent contribution, Martin and Denis report some observations on four patients with myelogenous leukemia, in whom analysis of the blood for non-protein nitrogen, uric acid, and creatinin were made both before and after radiation. They noted that the non-protein nitrogen fraction which was extremely high before treatment fell steadily after exposure to the rays. On the other hand, the uric acid content, also high before treatment, showed no appreciable decrease, notwithstanding the fall in the number of white cells which occurred as a result of röntgen-ray exposure. The creatinin content of the blood remained within normal

limits throughout. In view of the normal creatinin values and because in the most severe cases urea accounted for only 20 per cent of the non-protein nitrogen fraction, Martin and Denis suggest that the blood in leukemia contains, possibly as a constituent of the white blood-cells, some nitrogenous substance or substances not differentiable by our present methods of micro-blood analysis.

It has been shown that radium may exert an equally marked effect on the nitrogen and phosphorus metabolism in leukemia (Knudson and Erdos; Ordway, Tait, and Knudson). They observed in two patients with myelogenous leukemia, under radium treatment, very remarkable increases in the total nitrogen, urea nitrogen, ammonia nitrogen, and phosphorus. During the first seven days the total nitrogen excretion of one patient increased 115 per cent, the urea nitrogen 140 per cent, the ammonia nitrogen 150 per cent, the uric acid nitrogen 28 per cent, and the phosphorus 174 per cent. After the seventh day all of the excretory products showed a slight drop, but remained at a higher level than at the beginning of treatment. Subsequent applications of radium again brought about a rise in the elimination of these urinary constituents, the excretion of phosphorus exhibiting the most remarkable increase of all. Ten days following the third series of radiations the phosphate output had increased 445 per cent over the elimination of the first day of the experiment.

The comparatively low percentage increase in the uric acid excretion is surprising in view of the great destruction of tissue rich in nuclein material which is known to occur in leukemia. In explanation of this observation, it has been suggested that radium emanations, which have been shown to decompose uric acid in vitro (Sarvonat), may also bring about the same result in the body, possibly by activating the ferments concerned with the cleavage of uric acid (Gudzent and Loewenthal).

There is also a great paucity of data regarding the blood changes produced by radium in leukemia. Determinations of the non-protein nitrogen and creatinin of the blood in one patient during treatment showed only a slight increase of the former constituent and no change in the latter (Ordway, Tait and Knudson).

The nature of the process by which the röntgen-rays and radium produce their remarkable effect on metabolism is little understood. Most observers are inclined to attribute the changes in the nitrogenous metabolism to tissue autolysis, due either to the elaboration of certain toxins in the blood (Linser and Sick) or to the stimulating effect of both forms of radiant energy upon enzyme activity in general, and more particularly upon the enzymes which bring about proteolysis (Musser and Edsall; Sarvonat).

Benzol.—Like the röntgen-rays and radium, benzol exerts a destructive action not only on the parenchymal cells of the hemopoietic organs as a whole, but more especially on the myeloid tissue and the

circulating leukocytes derived from this tissue (Selling(*a*)(*b*)). As a result of these destructive changes, derangements of metabolism have been found, which, however, have been too little studied to make possible any definite conclusions concerning them. In some observations on three healthy individuals and on one leukemic patient, Sohn noted a reduction of the oxidative processes of the body. He found an increased output of neutral sulphur and ammonia, and a diminished percentage excretion of urea—metabolic changes which have been observed also in other severe intoxications. The uric acid elimination remained normal notwithstanding the great destruction of white blood-cells due to the leucotoxic action of benzol.

Döri, in a similar case, studied over a period of fifty days, determined the influence of benzol upon the excretion of nitrogen, creatinin and creatin. During the period of observation, the patient showed constantly a negative nitrogen balance, and an increased output of creatin and creatinin. The elimination of creatin was especially significant, and in view of the known relationship which exists between the elimination of creatin and endogenous protein metabolism, Döri is inclined to regard the increased creatinuria as the result of a toxic action of benzol on the body protein.

The Metabolism in Pathological Conditions of the Stomach and Intestines . . . . . *Thomas R. Brown and John H. King*

The Stomach—Function—Secretory Disturbances—Hypersecretion, Hyperchlorhydria, Hyperacidity—Hyposecretion, Hypochlorhydria—Subacidity, Achlorhydria, Achylia—Motor Disturbances—Metabolic Disturbances in the Various Gastric Diseases—Gastric Ulcer and Gastric Erosions—Carcinoma and Other Neoplasms of the Stomach—Gastroptosis Atony Dilatation—Gastric Neuroses—Gastric Disturbances in Other Diseases—Gastric Operations—The Intestines—Introduction—The Inflammatory Enteropathies—Appendicitis—Constipation—Enteropathies due to Alterations of the Lumen or the Position of the Intestines—Enteroptosis—The Parasitic Enteropathies—The Congenital Enteropathies—The Nervous Enteropathies—The Neoplastic Enteropathies—The Specific Diseases of the Intestines—Syphilis of the Intestines—Intestinal Disturbances Secondary to Diseases of the Stomach—Intestinal Disturbances Following Abnormality of the Ductless Glands—The Diarrhea of Exopthalmic Goiter—The Diarrhea of Addison's Disease.

The Metabolism in Pathological Conditions of the Stomach and Intestines

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The Stomach

Howell says, "Under the head of nutrition or general metabolism we include usually all those changes that occur in our foodstuffs from the time that they are absorbed from the alimentary canal until they are eliminated in the secretions." As the fundamental function of the gastro-intestinal canal is the preparation, digestion and absorption of the foodstuffs—protein, always above an irreducible minimum, this being dependent upon the especial tendencies, age, size, weight and activity of the individual so that always enough is present to repair the waste within the cells, fats and carbohydrate to furnish enough energy for the body's needs; salts, water, vitamines—it would seem that pathological conditions of the stomach and intestines should play a peculiarly large rôle in bringing about specific changes in the body metabolism. In reality, diseases of the digestive apparatus, with very few exceptions, have no apparent specific influence on metabolism such as is met with in diseases of metabolism proper, such as diabetes and gout, and in the ultimate analysis spell their effects by the influence of their associated secretory, motor and sensory disturbances, modified of course by the presence or absence of fever, anemia, infection, and processes of decomposition or fermentation upon the *general* nutrition of the body. Thus, as many gastric diseases of widely different etiology and even pathology, have many symptoms in common, so their effects on metabolism are very similar. For that reason it would seem wise to note the variations from the normal picture, especially as regards secretion and motor function—hypersecretion, hyposecretion, achylia, hypermotility, hyperperistalsis, hypomotility, etc.,—and to call attention at some length to the effect of such abnormalities upon metabolism, and to follow

this by a very brief survey of the various diseases of the stomach and the metabolic picture to be expected from the associated secretory, motor, absorptive and excretory abnormalities. And yet, due to the marvelous vicarious functioning of the intestines in gastric disease, it is remarkable how markedly diseased the stomach may be with little or no apparent effect on the general metabolism. In its finer details, however, we cannot help but feel that there must be minor changes in the finer mechanism of metabolism met with in variations in secretion, in motor function, in absorption and excretion and in bacterial flora and the products due to their growth and multiplication which are not recognizable by the comparatively crude methods at present in vogue and waiting for their elucidation for greater refinement in biochemical methods. As Friedreich Muller once said, "It is absurd to expect to solve the most complicated of body-processes by anything less than the *most refined* chemical methods" —and this, as many other problems in medicine, must wait for more intensive chemical and possibly physical methods for its explanation.

Function.—The function of the stomach is a manifold one—it acts as a reservoir for the ingested food, it breaks up and liquefies the less liquid portions, it aids in the digestion of certain foodstuffs, it propels the liquefied material and fluids into the intestine for further digestion and absorption, it plays a slight rôle in absorption and a more important rôle in excretion, it disinfects the food to a greater or less extent, although there is much difference of opinion as to the efficacy of the dilute hydrochloric acid as met with in the stomach in this connection. While many of its functions can be performed vicariously by the intestines, nevertheless the stomach must be regarded as an organ of real importance whose chief function is to spare the intestines, and which, if deranged by disease of considerable extent or of long duration, is likely to lead to nutritional disturbances unless excessive and often quite impossible care is given by the patient to the choice and preparation of the dietary, with the entire elimination of connective tissue as the stomach juices are absolutely essential in its proper digestion.

It is hardly necessary here to more than briefly touch upon the physiology of normal gastric digestion; the work of Pawlow, Bayliss, Starling and their followers has given us a clear picture of the secretory side and of the rôle played by the psyche, the appetite, the nervous apparatus, and by gastric hormones in this process, while the equally important work of Cannon, Carlson and others has given us a clear picture of the motor sphere under normal conditions. We have always felt that the weight of the evidence favored the view that the juice as secreted by the gastric glands is always of practically the same acid contents, its apparent variations being due to quantity, not quality, of juice secreted, to the varying admixture of food and saliva and gastric mucus, to variations in the motility of the stomach, and to the presence or absence

of regurgitated duodenal contents. The work of one of us seems to show the large rôle played by the degree of tonicity of the ingested meal in the ultimate condition of the gastric contents due to the marked effect of this tonicity upon the excretion from the stomach wall, hypertonic fluids provoking a marked excretory response. While it would take us too far afield to go into the subject deeply, reference must be made to the importance of the physicochemical explanation of the origin of the free hydrochloric acid in determining the chlorid content of the body in hyperchlorhydria and achlorhydria, and in cases where excessive amounts of sodium chloride are taken with the food, or where such intake is practically nil, with practically no influence upon the chloride content of the body but with marked variations in the chloride of the urine. As regards acidity, however, one of us has shown that there is no constant relationship between that of the gastric juice and of the urine, while the recent work of Stohl and King in determining gastric acidity in terms of ionization or hydrogen-ion concentration has really added to our knowledge of the relationship between acidity and peptic digestion. Although of importance in our consideration of this subject, we must leave to works on physiology the solution of other problems of importance in this field—the extent of protein digestion in the stomach; the presence of antiferment in gastric juice or in stomach wall as an explanation of the resistance of the stomach to autodigestion; whether pepsin or rennin are identical—although the weight of evidence is against this; the extent of fat digestion in the stomach and the reversible action of lipase and other ferments—these and similar problems make one realize the complexity of the digesting process, and the great possibilities, still in the main unsolved, of variation in the minor details of metabolism, even if in the majority of instances the major aspects may remain comparatively normal.

Variations in diet, as seen in different digestive diseases, notably the neuroses, carcinoma and ulcer, the marked lessening or increase in the intake of protein, of fats, of carbohydrates, of fluids and salts, if persisted in for a long time, must also produce certain special metabolic pictures, although as yet not studied in detail in reference to the various digestive diseases. According to Howell, "in the stomach it is possible that there may be absorption of the following substances, water, salts, sugars and dextrins that may have been formed in the salivary digestion or that may have been eaten as such, the proteoses or peptones formed in the peptic digestion of proteins or albuminoids," and although as a rule absorption does not take place readily in the stomach, variations in the degree of absorption must modify the metabolism, if only temporarily and in a minimal degree. The amount of hydrolysis of proteins, for example, must vary within very wide limits in different diseases of the stomach, depending not only upon the diet, but upon the secretory and motor activities of the stomach—here an achylia with hypermotility,

there hyperchlorhydria with pylorospasm and marked delay in emptying.

To again quote Howell, "The preliminary digestion in the stomach is important as regards the protein food from several standpoints.

"1st—In the matter of mechanical preparation of the food and its discharge in convenient quantities easily handled by the duodenum.

"2nd—In the more or less complete hydrolysis to peptones and proteoses whereby the subsequent action of the proteolytic enzymes of the intestine must be greatly accelerated."

The motor mechanism of the stomach is of course so arranged as to permit a very considerable diastatic action of the ptyalin of the saliva and the conversion of a considerable amount of starch into soluble products—and here again variations in secretory and motor functions as met with in different gastric diseases materially modify the extent of this digestion. Again the work of Mendel, Osborne, McCollum and others has added a new note of interest to the whole subject of nutritional disturbances in digestive diseases by their conception of the vitamines, essential to normal metabolism, and the lack of a realization that this factor plays a real rôle in the changes of certain dietetic treatments of certain digestive diseases—as for example the complete elimination of fruits and greens in the treatment employed by certain physicians for ulcer and enterocolitis. A lack of appreciation of the essential nature of these substances is certainly the cause of the obvious nutritional disturbances so frequently met with in patients who have been kept upon too narrow dietaries for long periods of time. We have, for example, seen several cases with scorbutic manifestations who have been treated with extreme qualitative dietetic rigidity for high grades of atony, ptosis and motor insufficiency, in which by the return to a better balanced dietary with fruit juices and green vegetables included, there was a rapid disappearance of the symptoms of scurvy, while nothing is so beneficial in the clearing up of the gastric and intestinal symptoms of pellagra as a marked increase of proteins and fats to the diet—usually markedly deficient in these ingredients. In fact the whole study of inanition and malnutrition must be in a sense rewritten in part by this comparatively new conception of a new and essential factor in the process. The study of the effect of deficiency in these essential substances has been rendered possible on a large scale by the war and post-war conditions of Eastern Europe and the work of Mellanby, Chick, Hume and many others has added immensely to our knowledge of the subject, notably in regard to scurvy and rickets, while McCarrison believes that he has shown that a deficiency of certain vitamines is the cause of certain gastric and nutritional diseases in many in association with a low protein and fat, high carbohydrate dietary, and that this new conception must be kept in mind in explaining the associated nutritional disturbances.

Secretory Disturbances

There is of course some question as to what constitutes an abnormality of gastric secretion, for even with the older but far more with the newer fractional methods it is noted that quite marked variations may be found in absolutely normal individuals with apparently absolutely normal digestion and varying, as also the motor functions, to a certain extent with the build of the individual, whether of the herbivor or carnivor type—both, according to Hurst, to be regarded as normal types. It is therefore with reference to a rather elastic normal that we define the secretory anomalies as hyperacidity, hypo- or subacidity and anacidity, hyper-, hypo- and achlorydria, or achylia, or perhaps better expressed as hyper- or hyposecretion, as fistula studies, as well as animal experiments, seem to show that the gastric juice has a practically constant acidity, this varying in different human beings between 0.35 per cent and 0.56 per cent. Most investigators agree that there is often, especially in pathological conditions, no parallelism between the amount of acid and pepsin-zymogen secreted, or between the latter and the chymosin or rennin-zymogen—perhaps the best argument against the identity of these two pro-ferments.

Hypersecretion, Hyperchlorhydria, Hyperacidity.—Notwithstanding the rather wide limits of normality, there are nevertheless a number of pathological conditions in which a real increase of acid occurs, either as a direct response to food stimulation or as a continuous process. This may occur as the gastric equivalent of a hypersthenic neurosis, or in certain organic diseases of the cerebrospinal apparatus; it is usually met with in the early stages of chronic gastritis due to a variety of causes usually acting over a long period of time, such as improper foods and beverages, alcohol, tobacco, highly seasoned foods, foods that are mechanically irritating, especially those imperfectly masticated, foods and beverages that are too hot or too cold, tainted foods, bacteria and their products arising from diseased gums, tonsils and the accessory sinuses; it is often of reflex origin, especially from pathological conditions elsewhere in the digestive tract, notably the appendix, although frequently from other sources, as a retroflexed uterus, an uncorrected error of refraction, etc.; it is met with in more than half the cases of gastric and duodenal ulcer, persistent hypersecretion being especially prevalent in the latter as well as in benign pyloric obstructions of various kinds and frequently in chronic appendicitis; it is not unusual in chronic constipation and intestinal stasis, while it sometimes appears to be of purely psychogenic origin. Whatever the cause, all present the same general picture, although varying in the individual case in extent and in duration—a real increase in the amount of acid secreted, probably *not* the secretion of a juice of higher acid content. In these cases, as a rule, there is a marked inhibition

of starch digestion, the protein digestion is more complete—this being often materially helped by the delay in emptying time of stomach usual in many of these cases—although here as in other secretory disturbances, the effect upon body metabolism is not so much a question of secretory anomaly as of associated motor disturbance and intestinal involvement. Even as regards bacterial growth in the stomach and the effect of high acid upon decomposition and fermentation, while it is unquestioned that increased acid has an inhibiting and possibly a truly disinfecting effect, it is again the state of the motor activity of the stomach that plays the major rôle, and if pyloric obstruction is marked, there may be considerable bacterial growth even with an excess of free acid. The ordinary putrefaction of protein does not, however, occur as a rule in these conditions, but carbohydrate decomposition—yeasts and sarcinæ probably playing the leading rôle with formation of alcohol, acetic acid and carbon dioxid as the more usual end products. These end products as they are absorbable should lead to *specific* metabolic changes, even if temporary and too slight to be recognized by the usual methods of examination.

Speaking generally, although there are many exceptions, increased gastric acidity is usually associated with a delay in emptying and constipation, which may in its turn lead to further delay in emptying time by a reflex pylorospasm and hypersecretion of gastric juice. As a general rule, the hyperacid gastric contents tend to lessen the fermentative and putrefactive processes in the intestines, while the diminution or absence of free hydrochloric acid in the gastric contents is usually associated with an increase in these processes.

Hyposecretion — Hypochlorhydria — Subacidity — Achlorhydria — Achylia.—The diminution or absence of hydrochloric acid, or of this and the pro-ferments as well, is met with in a great variety of conditions. It is often found in many infectious diseases, notably typhoid fever, and the late stages of tuberculosis; it is frequently associated with intestinal parasites, especially uncinaria; it is frequent in myocardial and renal disease; it is the usual picture in the later stages of chronic gastritis; it is not uncommonly found in gout, and is frequently met with in chronic infectious arthritis, although here the achylia is much more probably the effect, *not* the cause, of the disease, while in gout the administration of hydrochloric acid undoubtedly has a favorable influence on the purin metabolism in a certain proportion of cases. It is usually found in pernicious anemia, where according to a few observers it plays a real part in bringing about the characteristic hematopoietic and metabolic changes. In pellagra and sprue, subacidity, or oftener achlorhydria, is the rule, but in the one case the unbalanced dietary, in the other the marked change in intestinal mucosa and pancreas, possibly due to a monilium infection, unquestionably plays the major rôle in the profound nutritional disturbances met with, the achylia playing a minor part in increasing

the intestinal disturbances. In hyperthyroidism achylia or achlorhydria is frequently seen, as also in myxedema, and in the former probably plays a part in the diarrhea so often met with in that disease. In cancer of the stomach, and even in extensive carcinoma elsewhere, absence of free hydrochloric acid is the rule, except in that group in which cancer has developed upon an old ulcer base, while in linitis plastica, which many regard more as an acellular scirrhus than as a cirrhosis, absence of acid is the rule. In high grades of ptosis with atony achlorhydria or hypochlorhydria is the rule; in chronic gall-bladder disease lack of acid is frequently found. It is frequently seen as the expression of an asthenic neurosis, and peculiarly interesting are those cases of complete absence of acid after sudden shock or violent emotions, often temporary, but sometimes persistent, and associated with intractable diarrhea, often leading to quite marked nutritional disturbances.

According to the careful experiments of one of us, absence of free hydrochloric acid is not accompanied by a diminution in the pancreatic secretion, even though the acid-prosecretin mechanism is wanting, but the absence or diminution of acid must markedly affect the activities of the propepsin and chymosin, even if they are, as is seen exceptionally, not materially diminished as they both need free acid to become activated. There is apparently no connection between the amount of acid and of mucus secreted. In all cases starch digestion in the stomach is less impeded, while proteolysis is practically absent in cases of absence of acid, and diminished when the acid, although present, is found in much less amount than normal. In the case of connective tissue, the absence of hydrochloric acid means that this substance passes through the digestive tract practically undigested, and this is one of the causes of the associated diarrhea, often markedly improved by the elimination of meat from the dietary. The lessened protein digestion in the stomach, however, does not necessarily mean any protein loss by the body, provided that intestinal digestion be not impaired both as regards its secretory and its motor functions. In many cases, however, the marked decrease in the emptying time of the stomach—due more to patent pylorus than to increased peristalsis, so usually found in cases of diminished or absent hydrochloric acid—the far greater number of bacteria that reach the intestine and the improper preliminary preparation of the foodstuffs, both as regards digestion and physical properties, are likely to lead to enteritis of greater or less degree, sometimes associated with diarrhea, sometimes with constipation with a corresponding effect upon the digestion and absorption of food and the general nutrition of the body. In certain cases of the diarrhea so often found in achylias of various origin, notably the neurogenic or psychogenic group, an enteritis cannot explain the picture, which we have therefore felt might be caused by the need of free hydrochloric acid in the elaboration of some antiperistaltic hormone. Whatever

the cause of the diarrhea, if marked and of long duration, it is inevitable that malnutrition will take place often to a very marked extent, and nothing better illustrates the normal protective function of the stomach than this group of cases.

The specific influence of hyper-, hypo-, and a-chlorhydria upon the composition of the blood has not been definitely determined, although Von Noorden (*j*) (*g*) believed that the normal increase of alkalinity of the blood at the height of digestion was "particularly well marked in hyperacidity."

Notwithstanding the very considerable amount of work done upon the effect of secretory disturbances upon general metabolism with results often very conflicting, the question is still practically in the same state as when years ago Von Noorden wrote "disorders of gastric secretion, provided they do not prejudice the intake of food and are not complicated by motor disturbances of the stomach or disorders of the intestine, do not appreciably affect metabolism and the resorption of food, except that of connective tissue in cases of achylia."

Motor Disturbances

The three main functions of the gastric musculature are to preserve the proper tone, to furnish peristaltic movements of sufficient frequency, depth and force and to bring about a proper pyloric control, this last under normal conditions being affected by the character of food taken. The systematic employment of radiograph and fluoroscope has revolutionized our views of the motor activities of the stomach in health and disease; it has taught us the quite distinct functions of the cardiac sac and the gastric tube; the contractions met with in hunger; the antiperistalsis seen in pyloric obstruction, while as to the cause of the normal contractions Alvarez' views of the metabolic gradient are very suggestive.

Metabolism may be affected in many ways by motor disturbances of the stomach—by vomiting due to various causes, by motor insufficiency, by increased motility, by the associated secretory and sensory disturbances and by the effect of such disturbances upon the appetite, the intestinal digestion and the condition of the blood and urine.

Vomiting is a symptom of many gastric diseases, as well as being a frequent concomitant of other diseases—intestinal, renal, cardiac, neuroses, endocrine, etc. Its mechanism is usually a tight closure of the pylorus, marked peristaltic and later antiperistaltic waves, contraction of diaphragm and abdominal muscles and relaxation of cardia. Of gastric diseases, it is met with especially frequently in ulcer, in pyloric obstruction, chronic gastritis, carcinoma, neuroses and reflex pylorospasm due to a great variety of causes. If excessive or persistent it may lead to very marked nutritional disturbances, as the quantity of the food and fluid is markedly

diminished—aggravated by the increase in expended energy associated with the condition and the tissue-starvation acidosis with which the condition if at all marked is almost always associated, due to lessening of carbohydrate metabolism and increased destruction of fats, with lessened ability of the blood to carry carbon dioxid, and the formation of the acetone bodies.

In this as in many other conditions associated with an insufficient ingestion of food, such as lack of food, lack of appetite, fear of food, sitophobia, insufficient absorption of food, mechanical obstacles to the intake of food, neoplasm or stricture of the esophagus, cardiospasm, we meet varying phases of acute or chronic starvation, inanition with its caloric and its protein insufficiency, for with too little food the patient must live on his tissues, energy being furnished by the glycogen and fats, but with steady loss of protein from the less important organs if the protein intake be below the minimal requirements, this minimum being increased by fever, exercise, and lessened by rest. It is not necessary here to go into the details of the metabolic changes, the division of the tissue losses between protein and fat, the early utilization of glycogen and body fats, the later utilization of the proteins, the heart and nervous system living at the expense of the less important organs, the marked diminution in the chloride elimination in the urine, the later increase in calcium, phosphorus and magnesium. Absolute starvation is met with in certain diseases of the digestive tract—notably carcinoma at the cardia with complete obstruction —while partial inanition is very common in digestive diseases with diminution as a rule both of protein intake and total caloric energy; in all cases the metabolic changes are obviously dependent upon the degree of the starvation, although in certain diseases hunger and insufficient nourishment are relatively well borne, apparently due to a peculiar adaptability of the body to the abnormal nutritional conditions.

Hypermotility is the rule in the majority of the achylias, due in the main to the lack of pyloric tonus, as hyperperistalsis is often not associated with it, while in certain of the neuroses and in hyperthyroidism both hyperperistalsis and hypermotility are found. In other conditions, notably pyloric ulcer and acute or chronic appendicitis, hyperperistalsis but longer emptying time is the rule due to the associated hypersecretion and pylorospasm—the cause of many of the painful gastric symptoms met with in these conditions. Early carcinoma of the lesser curvature is not infrequently associated with hypermotility, while in duodenal ulcer either a true or a paradoxical hypermotility is usually met with, with as a rule marked peristalsis. In all these conditions the effect upon metabolism depends upon their effect upon the intestine, the presence or absence of diarrhea, enteritis, etc.

Motor Insufficiency represents a delay in emptying time, sometimes due to marked weakness of the musculature, congenital or acquired, oftener

to some obstruction at the pylorus due to a variety of causes—pylorospasm of local or reflex origin, ulcer, carcinoma, cicatricial contraction, pressure from diseased conditions of neighboring organs, gall-bladder, pancreas, mesenteric glands, etc., traction on a congenitally high pylorus by a markedly ptosed stomach, pyloric gumma, etc. If the motor disturbance is slight, the nutritional disturbance may be practically negligible, but if of high grade, the food remains for too long a time in the stomach, with, as a rule, perversion of secretion, decomposition, fermentation, and a fall of the food intake below the body requirements with increasing inanition leading to the picture of acute or chronic starvation, dependent upon the rate of development of the obstruction and the response of the gastric musculature to the increased work imposed upon it. It is the one condition of importance in which marked fermentation or decomposition is likely to be met with, the extent and character of these changes depending upon the degree of motor insufficiency and the associated derangement of secretion. In a certain group of cases the subsequent gastric dilatation simply represents the result of excessive work and the gradual weakening of the muscles under the strain, in others, changes in the wall due to the underlying process or the associated inflammatory changes play a larger rôle. Incidently the extent of motor insufficiency and gastric dilatation is not necessarily present in the same degree. It is very interesting to follow the gradual evolution of the symptoms in these cases, often first an increased appetite associated with the stage of compensatory hypertrophy, sometimes lasting a considerable time, sometimes gradually lessening, dependent upon the relative time of appearance of degenerative changes in the muscle and the character of the secretory disturbances, then fullness after meals, pain, vomiting sometimes after meals, sometimes at comparatively long intervals, increasing thirst, oliguria, increasing signs of malnutrition and tissue starvation unless appropriate treatment, usually surgical, is employed. The motor insufficiency due to weakness of the musculature due to intercurrent disease and increased by ptosis rarely reaches a high degree unless pyloric obstruction, sometimes due to low grade inflammatory process, sometimes to hypertrophy of the pylorus, develops. In cases of marked motor insufficiency if associated with considerable hydrochloric acid fermentation of the acetic-acid-alcohol type, in the absence of free acid of the lactic-butyric acid type may play some part in producing dilatation by distention but more by the effect of the products of decomposition upon the wall of the stomach.

While *increased motility* of the stomach has as a rule no influence upon metabolism unless associated with intestinal hypermotility, in *vomiting* and in *motor* insufficiency, if at all marked or of long duration, marked nutritional disturbances are bound to occur. Marked obstruction to the entrance of food into the stomach as in carcinoma or stricture of the

esophagus, or carcinoma of the cardia or even esophagospasm or cardiospasm may lead to marked symptoms of starvation, even resulting in the characteristic starvation-death if the obstruction is complete unless the condition is relieved by gastrostomy in some cases, by dilatation in others. Even in vomiting of *purely nervous* origin with no symptoms of obstruction at cardia or pylorus, profound nutritional disturbances may be met with; many of these cases of so-called nervous vomiting in reality represent an early phase of hyperthyroidism, which later develops with its characteristic metabolic disturbances.

The vomiting associated with organic obstruction of the pylorus plays, of course, the major rôle in the loss of weight and gradually increasing inanition as it is impossible for food intake to be sufficient for the body needs, although it is quite remarkable what marked grades of pyloric obstruction may be present with little or no vomiting, due to the compensatory hypertrophy of gastric musculature, and aided of course by careful choice of foods on the part of the patient—this again varying markedly in different individuals due to the different reaction of their stomachs to increased work—the ptotic individual being especially prone to early muscle weakening, stasis and dilatation; the individual with horizontal stomach with far greater powers of resistance and correspondingly later development of these conditions.

Motor insufficiency if of high grade always leads to marked nutritional disturbances, loss of weight and of strength, secondary anemia of the oligemic type, aggravated by the fermentative changes so frequently met with in obstruction, more marked as a rule in cases where free hydrochloric acid is absent. The absorptive powers of the stomach—never very great—are markedly diminished, while the decomposing material, the large masses of bacteria, yeasts, etc., when they do reach the intestines, as they must to a certain extent if the obstruction is not complete, lead to inflammatory changes in the intestines with concomitant disturbances in secretion, absorption and motor function. Whether certain of the striking symptoms sometimes met with in dilatation of the stomach—tetany, vertigo, etc.—are due to the absorption of toxins, to mechanical causes, to disturbance in calcium or chlorine metabolism with its effect on parathyroid function, to dehydration of the tissues, or to disturbance of the nerve supply, cannot be definitely determined—possibly all of these factors may play a rôle. The loss of chlorides from the body may be very marked if vomiting is persistent or excessive, especially in those cases with hypersecretion; the urine besides being decreased in amount may show a marked diminution in chlorides and its reaction may become alkaline, or it may contain the acetone bodies in abundance, and the patient show the typical symptoms of a starvation acidosis—this in turn markedly increasing the tendency to vomit.

Metabolic Disturbances in the Various Gastric Diseases

Gastritis.—In severe cases of acute gastritis, especially those of toxic or infectious origin and associated with enteritis, there may be rapid loss of weight and marked inanition, increased by the vomiting, diarrhea and fever so often present. In the ordinary chronic gastritis, on the other hand, due to long lasting indiscretions in food and drink, tobacco, or chronic infections of the mouth and accessory sinuses, it is surprising how long the condition may persist with no or very slight evidences of malnutrition, and here again the determining factor is whether or not the intestine is involved. In the late stages of chronic gastritis with achylia, such involvement is the rule, sometimes with diarrhea, sometimes with constipation and then considerable disturbances of nutrition are likely to be found. It is also surprising that in many cases notwithstanding the abnormal condition of the mucosa, how little the gastric musculature is affected, assuming of course that pyloric obstruction is not present. In the gastritis associated with pyloric obstruction due to ulcer, carcinoma, etc., it is far more the obstruction than the gastritis that affects metabolism.

Gastric Ulcer and Gastric Erosions.—There are many factors in gastric ulcer or gastric erosions, especially if pyloric, that affect body metabolism. If, for example, the intake of food is associated with pain, the patient develops a true sitophobia, and, although the appetite may be normal or even increased, this fear of eating may bring about such a diminution in the food intake as to lead to marked emaciation and often to the suspicion that the case is malignant. Whatever be the cause of ulcer, in more than 50 per cent of the cases in our experience hyperchlorhydria or hypersecretion is found, usually associated with pylorospasm, delayed emptying time and chronic constipation, often leading to mild nutritional disturbances. On the other hand, if food gives relief as in *duodenal ulcer* the intake of food is often increased and there may be even an increase of weight. In cases associated with frequent vomiting, notably *pyloric ulcers* with subsequent motor deficiency, nutrition may be very markedly affected, and in some cases the most extreme emaciation develops. If profuse hemorrhage or persistent bleeding takes place, we have the metabolic picture of a rapidly or slowly developing anemia superposed upon the picture. *Persistent pylorospasm* or *hourglass stomach* may affect the nutrition of the body by lessened intake of food due to pain, or by vomiting, or by its effect on the motor function. The motor function may be seriously affected if a contracting cicatrix is found or if perigastric adhesions develop or if inflammation or edema is present to a marked extent and if true obstruction develops, we have the picture of motor insuffi-

ciency already described. This picture, however, is in no way specific of ulcer, it simply represents a starvation phenomenon, whatever be the cause of the obstruction and the motor insufficiency; a gumma or an extragastric lesion producing the same degree of stenosis will bring about practically the same train of symptoms.

Carcinoma and Other Neoplasms of the Stomach

No other gastric disease has such an influence upon metabolism as carcinoma—the usual malignant neoplasm of this viscus—or sarcoma, which is extremely rare. Many factors play a part in this—the type of growth to a certain extent as the more cellular medullary and colloid forms are more likely to grow more rapidly and to ulcerate than the scirrhus form; the location of the growth, those at the cardia or pylorus due to their mechanical effects, leading to more rapid loss of weight and strength, and death from starvation unless surgical means are employed; the effect of the growth upon the appetite, this varying very markedly and often quite inexplicably, even when no obstructive phenomena are present, although as a rule loss of appetite, especially for meat, is a comparatively early symptom, the distaste for meat leading to certain disturbances in protein metabolism even when the total intake of food is sufficient for the energy requirements of the body. The nutritional picture differs somewhat in the primary cases and in those developing upon an old ulcer base—in the former achylia coming comparatively early, in the latter free hydrochloric acid, sometimes even in excess of the normal figures, being present for a considerable period of time. The tendency to spasm is not so great as in ulcer, the tendency to secondary gastritis and atony greater, while in some cases of carcinoma of the lesser curvature, hypermotility may be marked and the frequently associated diarrhea produce rapid loss of weight. In most cases, however, motor disturbances are not prominent except those due to obstruction. Usually anemia is present; often profound, and more often, the result of slight persistent bleeding rather than large hemorrhages, although in some cases it is hard to escape the conclusion that there is a toxic factor also present; in other cases secondary infection also plays a rôle. If high fever is present, usually the result of a severe secondary infection, in a few cases of rapidly growing neoplasms unquestionably due to a specific toxemia, we find the metabolic changes characteristic of fever—increased protein and fat destruction, especially changes in the blood, etc. In all cases associated with pyloric obstruction, motor insufficiency and stasis, decomposition of the gastric contents takes place, and if, as is usually the case, hydrochloric acid is absent, we find lactic and butyric and other organic acids, Oppler-Boas and other bacilli, sometimes yeasts and infusoria, with inevitable secondary

intestinal disturbances due to the bacteria and their products with a marked influence on intestinal secretion and absorption; apparently it is due to their influence upon gastric and intestinal digestion rather than to any *specific* effects that decomposition affects metabolism, and this seems equally true of the rarer products of decomposition or putrefaction sometimes met with, such as sulphuretted hydrogen, certain diamines, indol, acetone, etc.; thus we have heard of no case of sulph-hemoglobinemia secondary to putrefaction of gastric contents. These products of decomposition, however, undoubtedly affect gastric tone, and further impair the already seriously affected motor and secretory functions of the stomach, as well as markedly lessening the desire for food. Decomposition or fermentation is certainly less marked in those cases secondary to ulcer, for free hydrochloric acid is, next to an unimpaired motility, the most important factor in lessening bacterial activity, and in fact there is no tissue normally more proof against bacterial invasion than the gastric mucosa. There is certainly no proof that certain bacteria are absolutely pathognomonic of special disease processes.

A great deal has been written about the presence of a specific ferment in the cancer cells and in its secretions, the former bringing about marked cleavage in the protein molecule so that amino-acids may be found. Whether the cancer cells also secrete a specific toxin cannot be stated definitely although it is difficult to explain certain phenomena in a few cases except on this basis. As to the former, it is of interest to note that certain conditions associated with gastric cancer—increase of the soluble protein in the stomach contents, of antitrypsin in the blood, and of colloid nitrogen in the urine—are based on this conception, and this suggests that there are probably *slight specific* metabolic changes in this disease. The constant increase of the blood sugar as noted by Grove in a small group of these cases, is interesting in this connection. On the other hand, most of the component parts in the picture of cachexia, regarded as suggestive if not pathognomonic of this disease, can be explained by the secondary mechanical, secretory and motor disturbances, such as:

(1) Malnutrition and weakness from insufficient intake of food:
(2) Stagnation from mechanical obstruction to the pylorus;
(3) Secondary putrefaction associated with diminished secretion of HCl and ferments;
(4) Anemia from malnutrition, hemorrhage, infection;
(5) Insufficient absorption of food by either cancerous degeneration of important digestive glands or by secondary disease of the intestinal mucous membrane,

the site of the cancer and its rapidity of growth playing a fundamental rôle in this connection so that we may define cachexia as the characteristic

metabolic complication of cancer of the stomach while associated with it may be an acidosis varying in degree from a very mild to a very severe grade. The acidosis depends upon starvation for its production and is not a specific effect of the cancer itself.

In *gastric lues,* we may have a picture almost exactly simulating cancer, or less often ulcer, with obstructive phenomena, palpable tumor, usually gumma, bleeding and the usual nutritional disturbances of pyloric obstruction. It is essential to rule out gumma before we may definitely diagnose cancer, as the gastric secretory findings, motor disturbances and x-ray pictures may be practically identical in the two conditions.

In *gastric polyposis,* also, the repeated hemorrhages, obstructive phenomena, anemia and loss of weight and strength may again present practically the same local and general picture as cancer. While in certain cases the radiographs furnish suggestive evidence in favor of polyposis, sometimes only an exploratory laparotomy can make the diagnosis certain.

Gastroptosis—Atony—Dilatation

Ptosis of the stomach *per se* has no influence on metabolism. Nevertheless, the individual with downward displacement of the stomach, whether congenital or acquired, is unquestionably far more prone to develop atony and motor insufficiency than the person with horizontal stomach. This is especially true of those cases of ptosis associated with a congenitally high, relatively fixed pylorus and duodenum, as the traction on the pylorus, obviously increased by overloading the stomach, leads to constriction, partly due to spasm, partly to hypertrophy of musculature, partly to peripyloric adhesions. In certain of these cases, in which the tone has been further reduced by pregnancy and diseases associated with loss of weight, fever and inanition, the combination of lack of gastric tone with partial obstruction may lead to marked dilatation with a degree of malnutrition often as marked as that seen in the *late* stage of gastric cancer, and yet when a return to normal weight and strength may be brought about by persistent rest, posture, massage, careful diet with hyperalimentation as soon as that is possible, measures designed to improve nutrition, combined in some cases, if the pyloric obstruction is more organic than functional, by pyloroplasty. These cases of ptosis complicated by atony, motor insufficiency and dilatation show the same picture of chronic starvation as previously described under other forms of pyloric obstruction, and the ptosis is but a contributory factor in this picture. *Simple atony* has but little influence upon metabolism, but with the development of *motor insufficiency* of a more marked grade, nutrition is bound to be affected, the degree of this depending on the extent of the obstruction and of the loss of gastric tone and not upon the specific cause with the possible

exception of cancer. In the atony and motor insufficiency associated with high grades of ptosis, hypochlorhydria is the rule, real achylia very frequent, and the fermentation and decomposition met with may be practically the same as in obstruction due to gastric cancer, with, however, as a rule not the same amount of putrefactive changes.

Atony may develop secondary to gastritis of various causes. It may be due to long lasting wasting or febrile disease, it may be congenital, it may be neurogenic and represent a lack of balance between vagus and sympathetic, it may be secondary to pyloric stenosis due to a variety of causes, —but whatever its etiology, unless transitory it offers the substratum for subsequent serious motor disturbances with profound nutritional disturbances.

The *acute dilatation of the stomach* met with after operations, or during the course of certain infectious diseases, notably pneumonia and typhoid fever, has associated with it many symptoms the cause of which has not been definitely determined, notably tetany. The weight of the evidence, however, seems to be against this condition being an autotoxemia but rather in favor of a neurogenic origin or of its being due to duodenal obstruction, possibly a gastro-mesenteric ileus, or to acute gastric hypersecretion. None of the explanations is absolutely satisfactory, but whatever the cause, profound nutritional disturbances with acidosis occur, and often death unless relief is obtained.

Gastric Neuroses

In many cases of nervous affections of the stomach, nutrition is not affected, but in those in which the appetite is markedly affected, as anorexia nervosa, or when persistent vomiting is found, or where hypermotility is present and is associated with a corresponding condition of the intestines, nutrition is bound to suffer, and in some of the cases, notably anorexia nervosa and nervous vomiting, the intake of food may be so much diminished as to lead to marked starvation.

On the other hand, in the cynorexia or bulimia met with in certain neuroses, hysteria and mental diseases, as the manic phase of manic-depressive insanity, a very marked increase in food intake may occur with increased weight mainly due to increased deposition of fat, probably increased heat production, and an acceleration of general metabolism. The same picture is produced by the *overfeeding* used so extensively in the treatment of gastric neuroses, gastric atony or in states of malnutrition following various infections or surgical operations, in all of these conditions the weight increase being materially helped by the mental and physical rest which is usually insisted upon. Metabolism as well as weight is increased by such means, a real increase of activity of the body-cells,

this being especially helped by marked increase of the proteins in the dietary. There is nitrogen retention, the fats are stored up as fats, the carbohydrates as glycogen, while in protein overfeeding there is at first a slight increase in nitrogen excretion, but if the protein intake be not too great, there occurs an early adaptation by the body to the new diet. As to the increased heat production, Rubner believes it is due to the cleavage of the protein molecule into its nitrogenous and non-nitrogenous constituents.

Gastric Disturbances in Other Diseases

In a great variety of diseases apart from those of the stomach, the associated gastric disturbances often play a rôle in metabolism. In gout, we have often an achylia, as also in many *cardiopathies* and *nephritides* and this may play a part in nutrition, possibly as one of the factors in the diarrhea so frequently met with in the last two conditions. The *marked vomiting* sometimes met with in *retroflexion* of the uterus may produce considerable loss of weight, while this plays a similar rôle in many of the acute intestinal diseases, as appendicitis, although fever and infection probably play a larger rôle. *Vomiting* and *diarrhea* if present in *hyperthyroidism* adds to the loss of weight already caused by the endocrine disturbance. The gastric picture, achylia and often vomiting, plays its part in the nutritional disturbance of *pernicious anemia,* while the loss of appetite and frequent vomiting met with in acute infections unquestionably accelerate the loss of weight so characteristic of these diseases. The intractable vomiting of the gastric crises in *tabes dorsalis* mainly accounts for the rapid loss of weight during the attacks.

Gastric Operations

There is practically no abdominal operation that is not followed by rapid loss of weight and acidosis, the latter unquestionably lessened by the glucose-soda solution given by Murphy drip. This is peculiarly likely to occur after operations upon the stomach—*gastro-enterostomy, pyloroplasty, resection*—for in all these cases early starvation and underfeeding for a considerable period of time are essential if good results are to be expected. But in these operations other factors may influence nutrition—*large resections* are apt to be followed by diarrhea, but the fact that the intestine soon adapts itself to the new conditions if proper care is given to the dietary, illustrates anew the fact that gastric digestion is not essential. Gastro-enterostomies may be followed by vicious circle and persistent regurgitation of food which seriously affect nutrition and may necessitate a secondary operation, although to a certain extent the reflux of alkaline

fluid into the stomach is one of the causes of the comparative success of this fundamentally unphysiological operation, for almost all cases are followed by a greater or less degree of intestinal indigestion and in a few cases a jejunal ulcer may develop to affect nutrition by loss of blood, enteritis, diarrhea and vomiting.

The recent study of basal metabolism by the newer methods has not added much to our knowledge of nutritional changes in digestive diseases. It has shown that in the constitutionally inferior neurotic with nervous dyspepsia the metabolic rate is a little low. Cases associated with malnutrition also generally show a low metabolic rate; thus it is usually met with in cases with persistent vomiting, while in malnutrition associated with carcinoma the metabolic rate is low, although if we have one of the cases with marked toxic manifestations the rate may be, on the contrary, high. It has furnished us a satisfactory means of differentiating the vomiting and diarrhea of hyperthyroidism, in which the rate is high, from nervous vomiting and nervous diarrhea in which the rate is usually low, and it unquestionably may be of some value in showing the effect of the results on medical or surgical treatment, notably in cases where nutritional disturbances are an important feature.

By and large, however, the metabolism in digestive diseases is largely dependent upon the effect of the associated secretory and motor findings, the presence or absence of concomitant inflammation, infection or fermentation upon the nutrition, and it is practically impossible at the present writing to discuss specific metabolic changes from the standpoint of the individual organs. Perhaps nothing shows this better than the absolute dearth of literature on this subject.

The Intestines

Introduction

As the physiological processes of the intestine are so manifold and complex, it is to be expected that any attempt to correlate the complications arising from disturbances in their functions would be met with unusual difficulties. This is particularly true in regard to the disturbances in metabolism associated with diseases of the intestines, for the diseases of this tract have no specific metabolic complications. It is only through derangements of the physiological processes that the body metabolism is affected, and it will therefore be necessary to review briefly the physiological functions of the intestines which influence the metabolism of the body. In no other way does it seem possible to trace the somewhat indefinite metabolic complications resulting from diseases of the intestines.

The functions of the intestines are, in general, to complete the processes of digestion. This it does by carrying along further, the digestion of foodstuffs begun in the stomach. Associated with this, the intestines absorb the various foodstuffs, evacuate indigestible residue, and excrete waste products from the body. For the body metabolism to be normal, these functions must not be greatly disturbed. There is a certain amount of complementary functioning in the intestines which can carry metabolism along, if the disturbances are not too marked.

The functions of the small intestines differ somewhat from those of the large intestines. In the former the larger part of digestion of foodstuffs as well as absorption takes place. Very little absorption takes place in the large intestines and its main function is excretatory. The ferments, which by their digestive activity prepare the various foodstuffs for absorption, are largely secreted by the small intestines, in conjunction with the pancreas and liver, and it is in this part of the alimentary tract that the major part of the absorption of foodstuffs takes place. The colon practically plays a passive part in digestion. It absorbs water, but proteins and carbohydrates only to a small degree, and no fats. The lower part of the colon is mainly concerned with the excretion of salts and foreign substances, while the fermentation of carbohydrates is almost limited to this part of the intestinal tract. The intestines differ from the stomach in one important aspect, that decomposition normally takes place there.

The main functions of the intestines are then: secretion, absorption, excretion, decomposition and the mechanical elimination of fecal matter. These various functions are so closely interrelated that it is difficult to trace the part that each plays in intestinal diseases. For example: disturbances in secretion cause disturbances in absorption, while disturbances in absorption and secretion cause disturbances in peristalsis. So it is easy to conceive, with these various components of digestion disturbed, how difficult it would be to designate which factor is responsible for the effects observed upon the metabolism of the body. Such effects are produced largely through chemical and biological derangements, which influence especially the nutrition of the body. As there are similar chemical and biological disturbances in many diseases of the intestines, so the metabolic complications resulting are in many respects similar, differing largely in degree and not in kind, and concerning principally the nutrition of the body. Diseases of the intestines do not cause any specific derangement of the metabolism as occurs in diabetes and gout for instance. Furthermore mechanical factors, such as obstruction, the position of tumors, increased peristalsis, etc., play an important rôle in determining the extent, as well as the rapidity, of the disturbances of the metabolism.

The fact that there is practically no literature on the subject indicates the obscurity in which it is now veiled. This is largely due, no doubt, to

the difficulty in controlling the conditions which would be necessary to analyze the various disturbed factors. It would involve the control and analysis of such complex factors as absorption, excretion and ferment digestion. In addition these are so closely interrelated that it has been a discouraging task to try and unravel their complexity. These difficulties have, to an extent, kept experimental investigators from the field. Consider alone the complexity of the intestinal chyme. It contains:

(1) Gastric and pancreatic juices for the proteins.
(2) Bile and pancreatic juices for the fats.
(3) Saliva, pancreatic juices and succus entericus for the carbohydrates.

When the intestines are diseased there follow disturbances in the workings of the above-mentioned secretions and through such disturbances the metabolism may be affected. It is necessary to discuss briefly the results of such disturbances in the body metabolism. However, it is not within the scope of this article to deal broadly with the metabolic complications associated with disease processes in the accessory digestive glands, as the liver and pancreas, but only to touch upon the functions of these organs which are intimately associated with the intestines.

The bile secreted by the liver is closely associated with the absorption of fats and any marked retardation of its secretion causes a loss of fat to the body which may result in considerable disturbances in nutrition, such as loss of body weight. This occurs largely through the failure of the bile to render the fatty acids and soaps soluble and not through lack of emulsification of the fats. Such disturbance is often seen in severely jaundiced patients, in whom a considerable degree of loss of weight bordering upon emaciation may result.

The pancreatic juice must be absent over a long period of time to produce any effect on metabolism. When such a condition occurs, it is the absorption of proteins and fats that are mostly affected. Extreme grades of pancreatic insufficiency lead to most marked nutritional disturbances, through which the patient may eventually reach a state of true emaciation. It is in such conditions that marked grades of azatorrhea and steatorrhea occur. There is little known about the temporary insufficiency of the pancreatic juice or whether different grades of pancreatic insufficiency occur. Furthermore, there is no definite information regarding the effect of absence of the pancreatic juice upon the other digestive juices, nor upon the motility of the intestines. A certain amount of vicarious functioning by the intestines for the pancreas can take place, so that mild grades of pancreatic insufficiency may occur without symptoms or complications. However, long standing and complete absence of the pancreatic juice eventually causes death through emaciation, from the nutriment of the food draining away unused in the feces.

The succus entericus possesses two important ferments:

(a) Enterokinase which renders trypsin active.
(b) An amylolytic ferment, which can invert cane sugar and convert maltose into dextrose.

These ferments are essential for normal digestion. To what extent, impairment of their functioning influence the metabolism of the body is unknown. Certain it is that pepsin and erepsin can carry on the further digestion of proteins in the absence of trypsin, but only to a limited degree, as shown by the high protein content of the feces in marked grades of pancreatic insufficiency. How serious absence of the amylolytic ferment would be is a matter of conjecture, especially when we consider that the pancreatic juice itself and the saliva contain a ferment for the digestion of carbohydrates.

The bile, the pancreatic juice and the succus entericus then are intimately connected with the intestines in their various functions. Derangements may occur, primary in the organs elaborating these digestive juices and the intestines be secondarily affected, and through both, the metabolism influenced. Or the process initiating the disease may be primary in the intestines and the above considered secretions be secondarily affected. It is difficult to assign to any one of the secretions its exact rôle in the causation of the metabolic complications. Rather these secretions must be considered as a whole, by their combined functions regulating digestion and thereby having a definite influence upon the metabolism of the body.

Equally as important as the secretory functions is the motor activity of the intestines. Disturbances in the propulsion of the intestinal contents are associated often with striking intestinal upsets, which react to varying degrees upon the body metabolism. For absorption to be normal, the motor activity of the intestines must not be much deranged. Increased peristalsis perhaps interferes more with the proper absorption of foodstuffs than does delay in motility, unless the latter be very great and associated with either obstruction or very marked constipation. The extreme length of the intestines and its large absorptive surface permit fairly complete absorption of foodstuffs, in the presence of a moderate degree of hypermotility. Also the fact that the colon, under stress, can to a certain extent increase its rôle of absorption, gives the intestines a considerable power of protecting the body from deficient absorption. However, marked grades of hypermotility occur where the foodstuffs are so rapidly propulsed through the intestines that particles of food appear undigested in the feces a few hours after they have been taken by mouth. Such a condition may be met with in some of the achylia gastricas and naturally the nutrition of the body suffers markedly in such conditions.

Delayed motility of the intestines such as occurs in spasms, stenosis,

occlusions and complete paralysis of the bowel, introduce added factors, in that besides delay in excretion of the feces there may take place a considerable degree of decomposition and increased absorption. These factors will be considered when the diseases with which they are associated are taken up.

The absorptive function of the intestines is protected from marked disturbances by the fact that it is spread over such a wide area in the intestines. For absorption to be much affected in disease of the intestines, the lesion must be very widespread, especially in the small intestine. It is stated that one-third of the small intestine can be removed without harm, provided the diet is carefully regulated. Hypermotility disturbs absorption much more seriously than does disease affecting the intestinal mucosa, unless that disease be very extensive.

The intestines differ from any other organ of the body, in that decomposition takes place normally within its lumen. The intestinal chyme is easily subject to decomposition as is evidenced by the fermentation of carbohydrates, conversion of fats into lower fatty acids and the putrefaction of proteins. This normal amount of decomposition has no deleterious effect upon the body, because the products are in the main non-toxic, the amounts elaborated are not excessive and the motility of the intestines insures their expulsion from the body without undue absorption. Decomposition as a normal process in the intestines is largely limited to the large bowel and putrefaction is said never to take place above the ileo-cecal valve, except under pathological conditions. However, in disease, the occurrence of excessive putrefaction is followed by deleterious effects on the metabolism of the body and its discussion will be taken up when this phase of the subject is considered.

It can be therefore seen that as far as the intestines have an influence on the body metabolism their rôle is a complex one, more involved in the consideration of what particular disturbed function is responsible for the derangement than the type of disturbance caused. For the intestine is in a certain sense the chemical and biological laboratory of the body and its function is primarily to maintain the proper nutrition for the body. So when it is diseased, although the disease processes may vary markedly in their nature and cause, they have one thing in common that they disturb the nutrition of the body, no matter what other effects they may set up. For, although there are many diverse processes taking place in the intestines, their purpose is in the end to prepare the foodstuffs for absorption and to eliminate the unnecessary components of these foodstuffs as well as the waste material from the body.

So in enumerating the disturbances of metabolism associated with the diseases of the intestines, it will be found that disturbance in the nutrition of the body is the chief complication. Its repeated occurrence borders on the verge of monotony, were it not that, in many of the diseases, it is

the direct cause of death. The interest lies more in the analysis of which of the disturbed factors in the pathological intestines are responsible for the effects on the metabolism of the body.

The diseases of the intestines will be taken up largely in accordance with the classification as given in Barker's "The Clinical Diagnosis of Internal Medicine," Vol. III. This arrangement groups the diseases very conveniently for the consideration of metabolic complications. Where such complications are the same for different diseases of a group, they will be considered for the whole group and not for each subdivision separately. Thereby much needless repetition will be avoided.

The Inflammatory Enteropathies

(*a*) *Acute enteritis.*
(*b*) *Chronic enteritis.*
(*c*) *Ulceration of the intestines.*
1. Chronic duodenal ulcer.
(*d*) *Appendicitis.*

This classification includes the diseases of the intestines associated with diarrhea, other than the specific dysenteries (such as bacillary and amebic dysentery), and inflammatory conditions of the appendix. It will also be convenient to include acute colitis in this subdivision.

Although it is possible, by means of stool examinations and x-ray, to differentiate to some degree which part of the small intestine is especially involved, the metabolic disturbances are practically the same and are determined more by the intensity and extent of the inflammation than by its exact localization as in the duodenum, jejunum or ileum or colon. In the primary forms of the acute inflammatory enteropathies, besides the inflammatory reaction in the intestines, there may be toxic effects due to spoiled food or chemical irritants.

In the mild acute enteropathies the metabolism of the body is not much disturbed. There may be a slight loss of weight, which is rapidly restored as soon as the diarrhea ceases. Secretion and absorption are only temporarily deranged and the increased decomposition which accompanies some of these enteropathies is of slight degree and produces no deleterious effect upon the body metabolism.

In the very severe cases, particularly those caused by the ingestion of spoiled food, there may be striking metabolic complications. Very marked loss of weight and dehydration of the tissues occur when the diarrhea is profuse. The absorption of ptomains from spoiled food may produce severe prostration, often with collapse. In children especially, there is rapid loss of strength and collapse, as familiar in the clinical picture of cholera infantum.

In general, it is the nutrition of the body which is upset but there is no specific effect on the metabolism, peculiar to this group of diseases.

When the inflammation goes on to the chronic form the body metabolism may be only slightly affected or very strikingly, as seen in the condition occurring in infants spoken of as atrophia infantum. A condition of true marasmus develops in which the infant is reduced to skin and bones. The nutrition of the body is so interfered with that eventually emaciation and cachexia supervene with terminal lethal infections. The slighter grades of chronic enteritis lead only to moderate loss of weight and strength, associated with weakness, irritability and depression.

Ulceration of the intestines may be caused by many different processes. In fact the etiological factors are so numerous that Nothnagel has gathered them together into six groups. Only certain of these groups interest us here. The classification may be found in Barker's "The Clinical Diagnosis of Internal Medicine," Vol. III, page 548.

The effects of ulceration of the intestines upon the body metabolism are determined largely by its localization, its extent, and the complications which it causes, such as cicatrization, adhesions, perforations, hemorrhage and obstruction. There is no specific effect of the ulcer itself upon the body metabolism, unless it be in luetic ulceration when the spirochætæ may primarily develop there and secondarily invade the body, producing disturbances varying according to which of the systems of the body it attacks.

The ulcers which it is of importance to consider are those due to necrosis, as simple duodenal ulcers and peptic ulcers of the jejunum and ileum. The simple duodenal ulcer is generally located on the anterior wall and about 1 cm. distal from the pylorus. It is an unfortunate situation, for when it cicatrizes it is so apt to lead to secondary dilatation of the stomach and its position on the anterior wall permits of perforation directly into the peritoneal cavity. Again, the cicatrization can involve the papilla of Vater, producing obstruction to the outflow of bile with jaundice and obstruction to the pancreatic duct. Perforation and hemorrhage are particularly prone to occur in duodenal ulcer in contrast to gastric ulcers. However, on the other hand, malignant degeneration of duodenal ulcers is less common than in the gastric type. Peptic ulcers in the jejunum and ileum occur most commonly after gastro-enterostomies.

In the simple uncomplicated ulcer of the duodenum, the metabolism of the body is influenced to a varying degree, dependent upon the extent to which the abdominal pain, associated with it, interferes with intake of nutriment. In many cases the nutrition is but slightly influenced and the patient keeps fairly well nourished, with only moderate discomfort. On the other hand, the great pain associated with the ulceration may force the sufferer to live on a very insufficient diet and great loss of weight and strength result. When there is obstruction with dilatation of the

stomach and secondary vomiting, very little nutriment reaches the circulation, since the absorption of foodstuffs in the stomach is very slight. Malnutrition bordering upon emaciation may result, associated with varying degrees of acidosis. The mechanical position of the ulcer and not its pathological nature determines how much the metabolism of the body is injured. Of course, if the bile and pancreatic juices are blocked off from entrance into the intestines, marked disturbances in the absorption of fats and proteins result, which further intensifies the malnutrition. There is no specific effect, as far as is known, upon the metabolism, resulting from a damming back into the circulation of bile or pancreatic juice.

Perforation of a duodenal ulcer may lead to fatal general peritonitis, which is usually so rapid that it does not produce any special added effect upon the body metabolism. The same may be said in case of fatal hemorrhage. Perforation into adjacent viscera as the gall-bladder, the intestines, large blood vessels, or the thorax, while they produce very diverse and often fatal symptoms, do so without modifying the metabolic complications to any considerable extent. The obstruction resulting from cicatrization occurs so high up in the intestines that no considerable degree of auto-intoxication takes place, as does when the obstruction is situated in the ileum or colon.

Jejunal and ileal ulcers occur most commonly after gastro-enterostomy performed generally for a gastric or duodenal ulcer. When associated with much pain they may greatly interfere with the patient's taking a sufficient diet to maintain the body equilibrium, consequently a state of malnutrition develops, often necessitating secondary operations for removal of the offending cause.

When malignant degeneration of the ulcer takes place the features of emaciation and cachexia are added to the picture. The effects of cancerous degeneration on the body metabolism will be discussed at length when cancer of the intestines is taken up for consideration.

Appendicitis.—Acute appendicitis occurs too rapidly to have definite metabolic complications. Its deleterious effects are exerted upon the blood vascular and nervous systems rather than upon the factors which control the metabolism of the body. Only the chronic variety of appendicitis need be considered here. In this disease some complications may occur which have an influence on the body metabolism.

(1) Hyperacidity associated with pylorospasm can occur, producing sufficient discomfort to interfere greatly with the intake of food. Where these features are very marked the patient's revulsion to food may be as great as in gastric or duodenal ulcers, and as marked a disturbance of nutrition result.

(2) Cecal stasis, from adhesions, producing constipation often of a very obstinate degree with intestinal stasis, decomposition and auto-

intoxication, is a very deleterious complication of chronic appendicitis. The patients may become miserable invalids, who diet themselves to such a degree that they border on the verge of emaciation. As constipation is such a frequent complication of this disease it will not be amiss to consider that subject at this point.

Constipation.—A great diversity of symptoms and effects, on all the systems of the body, has been ascribed to constipation. However it is variously stated that simple constipation does not cause increase in decomposition in the intestines. Little is known to what extent and under what conditions normal decomposition products of putrefaction and fermentation can cause the phenomena of disease. It is further stated that the putrefactive products which occur only under pathological conditions and which may cause toxic effects on the body metabolism are very few.

The factor which mostly determines the severity of the symptoms associated with constipation, is high grade intestinal stasis, resulting in chronic toxemia. There has been a great deal of speculation as to the causative factors which produce the symptom complex of headache, lassitude and general malaise, referred generally to auto-intoxication. Some have thought it due to a toxin normally present in the intestines, but in excess in constipation. Others have referred the cause to an insufficiency of the protective mechanism of the liver, or a marked overgrowth of Gram positive, proteolytic anaërobes, or a perversion of the intestinal ferments. Attention has been called to what a slight change in molecular constitution is necessary to convert the normal amide bases met with in the digestion of proteins into products of greatest toxicity, as lysin to cadaverin, and arginin to putrescin.

The metabolic complications of constipation are generally referred to auto-intoxication and in this process acid intoxication was considered to be a very important factor. It is necessary here to consider the bearing of acid intoxication, as evidence in gastro-intestinal diseases, upon the body metabolism. In acid intoxication there occurs an overproduction of acids, the so-called acetone bodies Beta-oxybutyric acid, diacetic acid and acetone. They occur through interference with proper oxidation in the body. Of the various types of acid intoxication it is necessary for us to consider only two types.

(1) Carcinomatous acetonuria, which occurs in association with malignant degeneration in the intestines and is largely caused by insufficient assimilation of food, especially carbohydrates, in the latter stages of the disease. The acetone bodies are derived from the foodstuffs after absorption, or from the body tissue. The acetone bodies found in the intestinal tract are probably secreted into it, and do not represent acid bodies manufactured in the intestines by disease processes. Of course the intestinal tract by causing malnutrition and states approaching starvation favors the production of acetone bodies, but these bodies do

not represent a specific product of pathological processes in the intestines. It has been shown in a number of diseases of the intestines as enteritis, carcinoma, that the acetone bodies are decreased when carbohydrates can be taken and utilized in sufficient quantities by the body.

(2) The circulatory disturbances of the intestines are not associated with metabolic complications of any particular importance. The slight disturbances of the metabolism which do occur are too vague to permit of any special discussion.

Enteropathies due to Alterations of the Lumen or the Position of the Intestines

(*a*) *Acute intestinal obstruction.*
(*b*) *Chronic intestinal obstruction.*
(*c*) *Dilatations of the intestine.*
  1. *Dilatation of the ileum and ileal stasis.*
  2. *Acquired diverticula of the colon.*
(*d*) *Abdominal hernias.*
(*e*) *Enteroptosis* (*mechanical ileus*).

Acute obstruction of the intestines may arise from a mechanical occlusion or from a sudden loss of motor power of the intestinal wall (adynamic and paralytic ileus). When the obstruction is in the small intestine, the serious symptoms of abdominal pain, fecal vomiting and collapse appear early and death is rapid, unless the obstruction can be relieved, whereas, if the obstruction is in the colon, serious symptoms appear more gradually and a fatal outcome occurs more slowly. The higher up in the intestinal tract that the obstruction occurs the more serious is the disturbance to the body nutrition, since, when the site is lower down in the intestines, a greater area is left above for absorption.

To produce severe symptoms an obstruction must be fairly complete, because otherwise the fluid condition of the intestinal chyme allows a great deal of material to pass the site of obstruction. Many causes produce mechanical ileus, such as twists, kinks, strangulations, and intussusceptions. The effect on the metabolism depends upon the extent and position of the ileus and not upon the character of the cause. In paralytic ileus, the causes may be inflammatory, as in acute peritonitis, toxic as in sepsis, typhoid, pneumonia or uremia, or reflex, as in renal or biliary colic. Here the causative factor may modify the effect of the obstruction on the metabolism.

The means through which the serious symptoms of intestinal obstruction are brought about is still a matter of doubt. A brief discussion of this phase of the subject seems advisable, before considering the metabolic complications of this disease.

The older theories of splanchnoparesis, of reflex nervous action in the cardiovascular centers, and the bacterial invasion outward from the intestines into the peritoneum or blood, producing peritonitis or septicemia, may be dismissed without discussion.

At the present time the most popular explanation of the symptomatology of intestinal obstruction is that it is due to auto-intoxication. Without discussing in detail the various causes assigned for intoxication which accompanies intestinal obstruction, it may be said that at the present time there are considered to be two distinct but complementary factors in toxemia:

(1) The presence of bacteria in the obstructed gut.

(2) The presence of necrotic tissue, as a substance for the elaboration of the fatal toxin, through action of these bacteria.

The metabolic complications of intestinal obstruction are not synonomous with the fatal symptoms produced in this disease. In obstruction of the small intestines, changes in the metabolism are not prominent, because the disease progresses too rapidly. The cardiovascular and nervous systems are more vitally affected.

In chronic, slow obstruction, especially in the large bowel, a considerable disturbance of the body nutrition may result manifesting itself in loss of weight and various degrees of acidosis. When a malignant tumor is the cause of the obstruction profound nutritional disturbances may occur which will be discussed when tumors of the intestines are considered.

The search for a specific poison in the obstructed bowel has as yet not met with much success. Various substances as alkaloids, etc., have been described, but the proof of their specificity and their relation to the symptoms of intestinal obstruction is still unsettled.

The metabolic complications of intestinal obstruction are due to interference with the body nutrition, and manifest themselves as loss of weight, loss of strength, cachexia, emaciation, auto-intoxication and acidosis. They are the same, whether the obstruction is in the large or small intestine, provided the patient survives the disease sufficiently long to permit of their development. It is not known that there are any different toxic products in the small and large intestines nor is there any differential effect on the metabolism in obstruction of the large and small intestines. True, the symptoms and signs are sufficiently different often to permit of a fairly accurate diagnosis of the site, cause and character of the obstruction, but the effect on the metabolism is purely quantitative and not qualitative, in obstruction of the small and large bowel.

Diverticulæ of the intestines do not have any particular effect of the body metabolism, except that associated with constipation or fever and infection.

Hernias may by incarceration cause ileus and strangulation, when their effect on the metabolism of the body is secondary, due to the obstruction which they produce.

Enteroptosis.—Enteroptosis is not strictly speaking a disease, but a symptom group, associated with a dropping of the abdominal viscera. It may exist in the body for an indefinite time, without causing any symptoms, until the individual undergoes some physical or nervous strain. The component parts in the clinical picture vary in accordance with which of the viscera are ptosed, from the normal position. The effects associated with drooping of the intestines concern us chiefly. These are briefly:

(1) Constipation, resulting from sagging and kinking of the colon, with loss of tone of the intestinal wall. Severe grades of intestinal stasis may result, with the symptoms discussed under constipation.

(2) Spasticity of the colon with various grades of mucus colitis, causing spastic constipation. The congenital type of enteroptosis, which is the more important one, is generally associated with neurasthenia of varying grades. Furthermore, there is often in these individuals a lack of balance in the antonomic innervations, due to the occurrence of a sympathicotonic or a vagotonic state. The result of these abnormalities is that stasis in the intestinal tract causes more serious symptoms than it would in normally balanced individuals.

When the visceroptosis is extreme and the normal evacuation processes of the intestines are interfered with by either the occurrence of atonic or spastic states in the intestines, the effects on the body metabolism may be quite striking. A considerable loss of weight and strength can occur, causing the victims to reach the condition of deplorable invalids, poorly nourished and nervously bankrupt.

Ptosis of the other abdominal viscera may modify the clinical picture. The kidney may be displaced so greatly as to become subject to attacks of Dietl's crisis and intermittent hydronephrosis. Again the liver and spleen may drop to a considerable degree, causing secondary pressure effects or disturbances in their functions which it is not within our province to discuss.

In general the metabolic complications of enteroptosis are those caused by intestinal stasis, modified by the secondary effects due to an abnormally balanced nervous system. The subject has been sufficiently discussed under the head of constipation.

The Parasitic Enteropathies

(*a*) *Teniasis.*
(*b*) *Uncinariasis and anchylostomiasis.*
(*c*) *Strongyloidosis.*

(*d*) *Ascariasis.*
(*e*) *Oxyuriasis.*
(*f*) *Trichocephaliasis.*
(*g*) *Trichonosis.*
(*h*) *Myiasis.*

As a group these parasitic diseases are not associated with striking metabolic complications. A few of the individual infections, however, do produce metabolic disturbances and these will be briefly considered.

(a) *Teniasis.* Infection with the tapeworm may be entirely without symptoms, or very severe symptoms may result from harboring the parasite in the body. A tapeworm may largely use up the food supply of the host, it may irritate the mucous membrane of the intestinal tract or it may elaborate toxins which affect the body deleteriously. Severe anemia and nervous disturbances are met with in some cases, and in long standing infections there develops a considerable grade of emaciation.

(b) *Uncinariasis and Anchylostomiasis.* Hookworm infection, while it especially involves the blood-forming and nervous systems of the body, is also accompanied by marked deterioration of the nutrition of the body. The anemia and inferior mental states of individuals infected with this parasite is associated often with marked wasting of the body, giving the typical pot-bellied aspect to its victims. Development, mentally and physically, is greatly interfered with when the infection occurs at an early age, so that these patients often appear to be many years younger than they actually are. It is thought that when the disease occurs before puberty, the endocrine glands may be disturbed.

The other infections in this group are not associated with any metabolic complications, unless it be in trichiniasis, which may cause a considerable degree of cachexia in very severe cases.

The Congenital Enteropathies

(*a*) *Congenital Malposition of the Intestines.*
(*b*) *Hirschsprung's Disease, or Megacolon Congenitum.*
(*c*) *Persistent Meckel's Diverticulum.*

In this group, only the curious malady megacolon congenitum interests us. This condition is characterized by a high grade of dilatation of the colon, with thickening of all the tunics of the wall, especially the muscularis, with retention of often enormous quantities of feces. In long standing cases with progressively increasing retention of feces, a considerable degree of emaciation occurs. The nutrition is greatly interfered with and these patients present a remarkable clinical picture, of general emaciation, with a tremendously distended abdomen, in which

the outlines of the giant colon are plainly visible to the naked eye. On the other hand, it is surprising how long and how great an amount of fecal matter can be retained in these colons without producing any outward symptoms of disturbing the nutrition of the body.

The Nervous Enteropathies

(a) **Disturbances of Motor Innervation of the Intestines.**
  (1) *Peristaltic Unrest.*
  (2) *Hypermotility of the Intestines.*
  (3) *Paralysis of the Intestines.*
  (4) *Paralysis of the Sphincter Ani Muscle.*

(b) **Disturbances of Sensibility of the Intestines.**
  (1) *Hyperesthesia of the Intestines.*
  (2) *Neuralgias of the Intestines.*

(c) **Disturbances of Secretory Innervation of the Intestines.**
  (1) *Mucous Colitis.*

In this group metabolic complications are associated practically with only two of the subdivisions.

Hypermotility of the intestines may lead to a nervous diarrhea or to spastic constipation. Rarely are the effects sufficiently great or of such long duration as to cause much interference with nutrition. In the diarrheas associated with hyperactivity of the thyroid gland, and the condition of achylia gastrica, there may be serious interference with the proper nutrition of the body and very marked loss of weight and strength. These diarrheas are associated with hypermotility of the intestines, but will be discussed separately under their proper headings.

Mucous colitis is regarded by many authorities as a pure neurosis. A neuropathic tendency is considered to be an essential precursor of this disease. The actual acute attacks, in which there are painful spasms in the colon followed by the passage of mucus in the feces, are probably initiated by reflex causes, as chronic appendicitis, cholecystitis, gastric or duodenal ulcer, or the accumulation of fecal matter in a posted colon. Generally the sufferers from this disease are undernourished, pale and often present the visceroptotic habitus. When the disease is of long standing, marked grades of malnutrition may ensue, bordering on emaciation. The victims of this malady often diet themselves very rigidly, or are unable to take much nutriment, so that they are at times existing on a practically starvation diet. There is no specific effect on the metabolism in this disease. The malnutrition results from interference with the proper intake, digestion and absorption of the foodstuffs and not from any peculiarity of the disease itself.

The Neoplastic Enteropathies

(a) **Carcinoma of the Intestines.**
   1. *Carcinoma of the rectum.*
   2. *Carcinoma of the colon sigmoideum.*
   3. *Carcinoma of the intestinum cecum.*
   4. *Carcinoma of the duodenum.*

(b) **Sarcoma and Lymphosarcoma of the Intestines.**

(c) **Polyposis Intestinalis.**

Carcinoma of the duodenum is rare and the descending loop is most often involved. When the tumor occurs in the suprapapillary form, the clinical picture resembles pyloric stenosis. The most frequent site of carcinomatous growth in the large intestines is the rectum, and then in order of frequency the sigmoid, the hepatic and splenic flexures and the cecum.

The chief metabolic disturbance caused by cancer of the intestines is cachexia. There has been a great deal of discussion as to whether the cancerous tissue itself exerts a specific effect on the body metabolism by means of a specific toxin, or whether the cachexia results entirely from diminished intake of food, secondary disease in organs which play an important part in metabolism, and increased bacterial activity.

Secondary secretory, motor and absorptive disturbances can explain many of the component parts in the picture of cachexia.

(1) Malnutrition and weakness, from insufficient intake of food.

(2) Stagnation and decomposition, from mechanical obstruction.

(3) Anemia, from malnutrition and hemorrhage.

(4) Insufficient absorption of food, from either cancerous degeneration of important digestive organs or from secondary disease of the intestinal mucous membrane.

Cancerous tissue contains an autolytic ferment which is capable of digesting body tissue, and this has been suggested as the specific toxic agent in cancer. The proof is still wanting.

Differences in the variety of cancer as adenocarcinoma, medullary, scirrhous and colloid carcinoma show no qualitative differences in their effect on the body metabolism. The speed of growth, their localization, and the character and site of their metastases determine the rapidity of the cachexia, rather than any inherent differences in the tumors themselves.

Acidosis of varying degrees may accompany the cachexia of cancer of the intestines. It depends upon starvation for its production and is not a specific effect of the cancer itself.

Metastases and invasion to other organs of the body may add new components to the picture, dependent upon the organs involved. Should

these organs have a specific metabolic function, as the pancreas, the liver or the ductless glands, then the metabolic effects resulting from disturbances in their functions will be added to the cachexia.

Sarcoma and Lymphosarcoma of the Intestines.—These tumors are less frequent than carcinoma but often grow more rapidly. They lead less often to obstruction, except when situated in the rectum. Their effects on the body metabolism are in general similar to those of carcinoma.

The Specific Diseases of the Intestines

Tuberculosis of the Intestines.—The metabolic feature of this disease are in general those associated with tuberculosis. The disease may be rarely primary in the intestines and regarded as simple chronic catarrh. Often it is only when emaciation supervenes, or spontaneous hemorrhage from the bowel occurs, or signs of pulmonary tuberculosis become apparent, that the true nature of the disease is suspected. When the disease involves the cecum, a considerable narrowing of the intestinal lumen may occur, adding the feature of intestinal stasis to those of tuberculosis itself. The general metabolic effect is emaciation, to which the intestines may add that of intestinal stasis with toxemia.

Syphilis of the Intestines.—This disease affects mainly the rectum, where it produces a slow growing stricture with symptoms of obstruction of the lower bowel. Rarely there occurs an enterocolitis of specific origin associated with ulcers, diarrhea and wasting. The metabolic complications are those caused by the syphilitic process itself, which may have affected many of the organs of the body. The disturbances, which the intestinal components of the disease cause, are those associated with intestinal stasis.

Intestinal Disturbances Secondary to Diseases of the Stomach.—There is a very striking clinical condition, characterized by profuse and frequent watery discharges from the intestines, associated with complete absence of hydrochloric acid in the stomach. The symptoms are largely intestinal, and the fecal movements may contain whole particles of undigested food matter. The movements may be as many as ten to twenty a day. If the disease has existed for any considerable length of time, marked loss of weight and strength result, the patients presenting a clinical picture suggesting malignancy of the intestines. There is marked hypermotility of the intestines, so much so that there is little time for digestion by the intestinal ferments, or absorption by the intestinal mucous membrane to take place. In what way the absence of hydrochloric acid produces this condition is not known. It is not through influence upon the bile or pancreatic ferments, for they are normal in this condition.

The suggestion has been put forward that there is an elaboration of abnormal peristaltic hormones. The state of malnutrition which develops in this disease is due to interference with digestion and absorption.

Intestinal Disturbances Following Abnormality of the Ductless Glands

1. **The Diarrhea of Exophthalmic Goiter.**—The diarrhea which may occur in this disease is often so striking that the clinical picture suggests an intestinal disease. Often the fact that the primary disturbance is in the thyroid is entirely overlooked. The movements are fluid, bile tinged and often contain food fragments a few hours after they have been eaten, indicating an increased peristalsis of the stomach and intestines, in addition to impaired digestion. The diarrhea may be transitory, periodic or permanent and appear at the early or late stages of the disease. Again, it may occur synchronously with the acute exacerbations of the disease and markedly increase their severity. The disturbance to the body nutrition, which can be very great, has two factors. The hyperactive thyroid gland increases the basal metabolism, causing a considerable loss of weight in severe cases. When diarrhea complicates the disease, still greater loss of weight and strength occurs, often reaching extreme grades. While the primary cause lies in the property of the overstimulated gland to accelerate the body metabolism, at least as great, if not, in some cases, greater interference with the metabolism results from the disturbed motility and absorption in the intestinal tract.

2. **The Diarrhea of Addison's Disease.**—Diarrhea may occur in crises of great severity in this disease, without obvious cause and often associated with spasm in the calves of the legs. In fact the clinical picture suggests a severe intestinal disturbance. The diarrhea takes the form of frequent watery discharges with colicky pains and may lead to collapse, delirium and coma. The abdomen is retracted, tense, the pulse small and the general picture suggestive of peritonitis. Great loss of weight and strength, amounting to severe grades of emaciation, may characterize the terminal stages of this disease, whose etiology is not always clear and which may be mistaken for severe intestinal infection. The deleterious effect on the metabolism of the body can to a large extent be due to the disturbed intestines.

There is then a great similarity in the effects on the metabolism, produced by diseases of the intestines. In the main, the chief disturbance is to the nutrition of the body, caused by interference with secretory, absorptive and digestive processes of the intestines and complicated by infective and putrefactive changes. The intestinal tract, which so largely controls the metabolism of the body in health, through its complex physi-

ological activities exerts, when diseased, no specific effect on the body metabolism. Its characteristic effect on the metabolism of the body is to cause various grades of disturbance in nutrition, dependent on how greatly its physiological processes are interfered with.

The Physiological and Pathological Chemistry of the Liver . . . . . *Louis Bauman*

The Normal Chemistry of the Liver—The Liver and the Carbohydrates—The Liver and Fatty Acids—The Liver and Proteins—The Detoxicating Function of the Liver—Bile—Bile Pigments—Cholesterol—Fat—Mineral Substances—Tests of Liver Function—Pathochemistry of the Liver—The Liver Functional Tests in Disease—Jaundice—Acute Yellow Atrophy—The Composition of the Liver in Acute Yellow Atrophy—Cholelithiasis.

The Physiological and Pathological Chemistry of the Liver

LOUIS BAUMAN

NEW YORK

The Normal Chemistry of the Liver

The liver is concerned with the secretion of bile and with the chemical transformation of substances in the blood which is supplied by the portal vein and hepatic artery. Much of the material absorbed from the intestines encounters the activity of the liver cells before it reaches the cells of the body generally.

The Liver and the Carbohydrates.—Glucose, fructose and galactose, which result from the enzymatic hydrolysis in the small intestine, of starch, saccharose and lactose, respectively, may be condensed by the liver and stored as glycogen. A variety of cells throughout the body can condense glucose to glycogen, but the formation of glycogen from fructose and galactose seems to be a special function of the hepatic cells. By means of its glycogenic function, the liver can prevent an accumulation of sugar in the blood and, conversely, it can supply glucose to the blood by rapidly hydrolyzing glycogen by means of its amylolytic ferment. By this mechanism the constant glucose concentration in the blood is assured. The glycogenic function of the liver is controlled by the sugar center in the medulla through its afferent and efferent nerves (vagus and splanchnic). Adrenalin, thyroid, various acids, phosphorus and other substances accelerate the rate of glycogen cleavage by the liver. The glycogen content of the liver varies with the diet and muscular activity of the organism; the liver of a dog under ordinary conditions contains from 2 to 4 per cent of glycogen, but it may contain 20 per cent, if carbohydrates are pushed to excess. Several authors have noted the disappearance of sugar from the blood after extirpation of the liver and in Eck fistula dogs, that had been starved and then poisoned with phlorhizin (Erdelyi, Mathews and Miller). In the latter, the liver was found to be glycogen free. The presence of glycogen in the liver prevents the deposition of fat therein and protects the organ from the deleterious influence of chloroform, alcohol, phosphorus, arsenic and bacterial toxins (Davis and Whipple, Graham,

Opie and Alford, Rettig); feeding carbohydrates before administering chloroform or salvarsan may therefore be a desirable prophylactic procedure (Bailey and Mackay). The formation of sugar from glycerol, glyceric aldehyde and lactic acid and the degradation of glucose to lactic acid have been observed during perfusion of the surviving liver of the dog (Barrenscheen). Considerable amounts of lactic acid are formed on perfusing a glycogen rich liver, but little or none is formed when the liver is poor in glycogen (Embden and Kraus).

The Liver and Fatty Acids.—The normal liver contains about 2 per cent of fat. In phlorhizin glycosuria, diabetes, starvation, acidosis, phosphorus poisoning and in other conditions, the liver may contain as much as 70 per cent of glycerides that have all the chemical properties of ordinary depot or stored fat. In this regard the liver differs from all other organs for these contain fatty acids which are more desaturated than those of adipose tissue. It appears to be the function of the liver to desaturate fatty acids, possibly to synthesize them into phosphatides, and thus to prepare them for utilization by the cells of the other organs of the body. Le Count and Long found that the fat-lecithin ratio is similar in fatty and normal livers but that the cholesterol-fat ratio is higher in the former.

Embden and his pupils, as well as Friedmann(*d*), have shown that of the fatty acids from acetic to decoic, those with an even number of carbon atoms are readily oxidized to acetoacetic acid by the surviving liver, but not by the kidney or muscle. They found that when glycogen was present in the liver the formation of acetoacetic acid was inhibited. Dakin and Wakeman have described two ferments in the liver; the one reduces acetoacetic to hydroxybutyric acid, and the other accomplishes the reverse reaction.

$$CH_3COCH_2COOH \underset{O}{\overset{2H}{\rightleftharpoons}} CH_3CHOHCH_2COOH$$

In ordinary conditions of health acetoacetic acid is further oxidized, probably by way of acetic acid, but in the absence of carbohydrate or when carbohydrates cannot be utilized, then acetoacetic and hydroxybutyric acids are formed in such quantities that they accumulate in the blood and tissues and lead to the condition known as acidosis. Many observations speak for the important rôle of the liver in the degradation of fatty acids. By oxidation, the liver first desaturates the higher acids, such as stearic and palmitic, then breaks them up into fragments which yield acetoacetic acid and this is ordinarily burned to carbon dioxid and water. The rapidity with which the liver turns to fats when carbohydrates cannot be utilized or are not available is well illustrated in the recent work of Embden and Isaacs. These observers found that the surviving liver of a depancreatized dog cannot convert glucose into lactic acid, but oxidizes fat

instead, which results in a marked increase of acetoacetic acid. The rôle of the liver in the production of acetone bodies is also well illustrated by the work of Fischler and Kossow, who studied the effect of the combined action of hunger and phlorhizin on Eck fistula and "reversed" Eck fistula dogs. (The "reversed" Eck fistula is made by ligating the inferior vena cava just above its anastomosis with the portal vein. The blood of the lower extremities and of the abdominal viscera is thus diverted into the portal vein and made to circulate through the liver and this, according to Fischler, greatly stimulates the functional activity of this organ.) It was observed that under these conditions the Eck fistula dogs excrete a small quantity of acetone bodies, the normal dogs excrete a larger quantity, and the reversed Eck fistula dogs excrete the greatest amount.

The Liver and Proteins.—From 10 to 25 per cent of the total nitrogen of the liver is in the form of connective tissue; from 45 to 65 per cent is contained in the albumin and hemoglobin fractions; and from 25 to 30 per cent is in the globulin fraction. During autolysis, the last fraction is digested, exclusively (Bradley).

The liver takes an active part in the deaminization of amino acids that result from the enzymatic cleavage of protein in the small intestine; it is also concerned with the conversion of the liberated ammonia into urea and with the further oxidation of the deaminized acids. The amino acids leucin, tyrosin, phenylalanin (Embden and his pupils), histidin (Dakin and Wakeman) and tryptophan (Homer), are oxidized to acetoacetic acid, when perfused through the surviving liver. The bulk of the carbon of the amino acids is synthesized into glucose and it is probable that the liver is chiefly concerned with this process. That the liver can synthesize urea from ammonia is now admitted by all investigators. Normally, basic ammonia is converted into neutral urea, but when necessary, part of it may be diverted to neutralize acetoacetic, betahydroxybutyric or other acids. The importance of this activity in the regulation of the acid-base equilibrium is clear.

The following experiments illustrate the importance of the liver in protein metabolism. Fischler observed that when Eck fistula dogs were fed with large quantities of meat they developed poisonous symptoms such as ataxia, catalepsy, amaurosis, coma and convulsions coincident with the secretion of an alkaline urine and saliva. These symptoms could be prevented by the administration of phosphoric acid. Fischler ascribes this condition to an alkalosis which results from the incomplete conversion of ammonia into urea. The same author noted that when Eck fistula dogs were starved and then injected with phlorhizin they also developed coma and convulsions, but now the ammonia and urea excretion was decreased. These symptoms are ascribed to toxic substances which result from the imperfect oxidation of amino acids.

Van Slyke and Meyer(*c*) have shown that after amino acids are in-

jected into a dog they accumulate in all the tissues, but disappear most rapidly from the liver, coincident with an increase of the urea concentration in the blood. Van Slyke, Cullen and McLean have shown that the urea content of the blood of the hepatic veins is from 2 to 20 per cent higher than that of the portal vein. A similar elevation of the urea content in the blood that had passed through muscle did not occur.

By virtue of its ferment arginase (Dakin and Kossel) the liver is able to directly convert arginin into urea and ornithin.

$$\begin{array}{l} NH_2 \\ | \\ C{:}NH \\ | \\ HN{-}CH_2CH_2CH_2CHNH_2COOH + H_2O = NH_2{-}CO{-}NH_2 + NH_2 \\ CH_2CH_2CH_2CHNH_2COOH. \end{array}$$

The synthesis of amino acids from keto acids by the surviving liver has been demonstrated by Embden and Schmitz(*a*)(*b*). These authors found that pyruvic acid was converted into alanin, phenylpyruvic acid was converted into phenylalanin and hydroxyphenylpyruvic into tyrosin. Alanin was also obtained when ammonium chlorid was perfused through a glycogen rich liver (Fellner). The liver therefore can synthesize amino acids from carbohydrate derivatives and ammonia and this may account, in part at least, for the sparing action of carbohydrates on protein metabolism.

Recent observations indicate that the liver is also concerned with the formation of fibrinogen.

The Detoxicating Function of the Liver.—The liver is partly concerned with the detoxication of poisonous substances absorbed from the intestine. The action of intestinal bacteria on proteins results in the formation of phenols, indole derivatives and amines, and these are absorbed and brought to the liver where they are chemically altered into harmless substances, either by oxidation or by conjugation, or by both processes. Phenols are directly combined with sulphuric acid, while indol is first oxidized to indoxyl and then united with sulphuric acid. These compounds are excreted by the kidneys and constitute the ethereal sulphate fraction in the urine. In Eck fistula dogs the sulphur partition in the urine is normal (Lade), and if cresol or indol is administered, an increase of the ethereal sulphate fraction results; therefore it is improbable that the liver is alone concerned with the formation of ethereal sulphates. Herter and Wakeman have shown that hashed liver tissue disposes of indol and phenol to a greater extent than other organs. Embden and Glaessner found that the surviving liver of the dog can synthesize ethereal sulphates, though the lungs and kidneys also possess this power to a lesser degree. The liver detoxicates benzoic acid by uniting it with glycocoll to

form hippuric acid as shown by the experiments of Friedman and Tachau, and Lackner, Levinson and Morse. Certain drugs, such as camphor and menthol, are combined with glucuronic acid by the liver, and thus rendered harmless. Metals such as copper, arsenic, mercury are combined and stored in the liver.

Ewins and Laidlaw have shown that the surviving liver can convert hydroxyphenylethylamin into hydroxyphenylacetic acid. Guggenheim and Loeffler have further shown that phenylethylamin, hydroxyphenylethylamin, indolylethylamin and imidazolylethylamin are deaminized and oxidized by the liver; thus these poisonous products resulting from the action of the intestinal bacteria on amino acids are rendered harmless by conversion into the corresponding alcohols and acids. Eustis has also observed that the liver of the turkey buzzard can detoxicate histamin.

The chemical changes which the amins undergo in the liver may be formulated as follows:

$$R{-}CH_2NH_2+H_2O=RCH_2OH+NH_3 \qquad RCH_2OH+O_2=RCOOH+H_2O$$

The detoxicating action of the liver on alkaloids is well known; when administered to Eck fistula dogs they escape the liver and produce a more profound effect than when administered to normal dogs.

BILE

The Composition of Human Bile (Rosenbloom)
(parts per 100)

	Liver Bile	Gall Bladder Bile (Hammarsten)
Bile salts	1.01	9.7
Mucin and pigments	.485	4.19
Cholesterol	.261	9.86
Fat	.685	.19
Soaps	.26	1.12
Lecithin	.642	.223
Total solids	2.98	17.0
Inorganic matter	.92	
Water	97.0	82.9
Fatty acids	.12	

Human bile is continuously secreted by the liver; it is stored in the gall bladder and is intermittently ejected into the small intestine as a result of the contraction of the muscle of the gall bladder and relaxation of the sphincter of the common bile duct. This effect is probably due to secretin, which is liberated by the action of hydrochloric acid of the chyme on the intestine. The daily excretion of bile in the human varies considerably. The average excretion is probably in the neighborhood of 800 c.c. In the dog, 200 to 300 c.c. are excreted each day. The ingestion of proteins stimulates the flow of bile more than do other foods. Bile

salts exert a distinct cholagogue effect, and as they are continually absorbed from the intestine a physiological stimulation of bile secretion is maintained. During its sojourn in the gall bladder the water content of the bile is decreased and mucin and calcium salts are added. The urea content of the bile is similar to that of the blood.

Bile Salts.—The sodium salts of taurocholic and glycocholic acids (the latter predominates in human bile) and of desoxycholic acid are present in the bile. Ordinary cholic acid has 3 hydroxy groups ($C_{23}H_{36}(OH)_3COOH$), while desoxycholic acid, as its name implies, has 2 ($C_{23}H_{37}(OH)_2COOH$). The derivation of cholic and desoxycholic acids from cholesterol has been definitely established by Windaus. The salts of the bile acids are soluble in alcohol but insoluble in ether, and these properties are utilized in the process of their isolation. They are further characterized by their reaction with furfurol in the presence of concentrated sulphuric acid, the so-called Pettenkofer test. At present there is no evidence that bile acids are formed elsewhere than in the liver. The bile salts, especially those of desoxycholic acid, form soluble addition compounds with the fatty acids from stearic to formic. Cholesterol also becomes soluble in the presence of bile salts (Wieland). The importance of this property in the digestion and absorption of fats and cholesterol is apparent. It is possible that the bile salts keep the cholesterol in bile in solution. Wieland has shown that desoxycholic acid is toxic for heart and striped muscle. Dog bile contains taurocholic acid almost exclusively, and of this about 2 or 3 grams are excreted each day. When taurocholic acid is administered to a dog, it is excreted fairly rapidly in the bile and stimulates its flow (Foster, Hooper and Whipple). Eck fistula dogs excrete only about one-half the normal amount of bile acids. The administration of cystin to a bile fistula dog is followed by an increased secretion of taurocholic acid.

$$\begin{matrix} S{-}CH_2{-}CHNH_2COOH \\ | \\ S{-}CH_2{-}CHNH_2COOH \\ \text{(Cystin)} \end{matrix} \longrightarrow 2NH_2{-}CH_2{-}CH_2{-}SO_3H \quad \text{(Taurin)}$$

Feeding cholesterol or red cells is without effect.

Bile Pigments.—The chief pigment of human bile is bilirubin. Bilirubin is a pyrole derivative closely allied to hemoglobin. It dissolves readily in warm chloroform and dimethylanilin, but is sparingly soluble in most of the other organic solvents. It can be obtained in crystalline form and is readily oxidized to biliverdin even by the oxygen of the air. It is acidic in nature and forms an insoluble salt with calcium. The average daily excretion of bilirubin by dogs is about 140 milligrams. According to Paton and Balfour human bile contains from 0.4 to 1.3 grams of bilirubin per liter.

When bile pigments are injected into the blood they are quickly excreted by the liver. An increased destruction of red cells within the body or the injection of hemoglobin is followed by an increased secretion of bilirubin. There is considerable evidence to show that bilirubin is derived from hemoglobin. Hemoglobin is probably disintegrated by the Kupfer cells which line the blood spaces of the liver, its iron is utilized anew, while the hematin is converted into bilirubin. Whipple and Hooper (*b*) have shown that under certain experimental conditions, tissues other than the liver can form bile pigment from hemoglobin.

In the large intestine, bilirubin is reduced to urobilinogen and urobilin and these are partly reabsorbed and brought to the liver, so that one may speak of a circulation of bile pigments.

Cholesterol.—$C_{27}H_{46}O$ is a terpene derivative, containing one secondary alcohol group. It is an unfailing constituent of all cells and is excreted in the bile in quantities varying from 0.24 to 0.59 gram per liter (Bacmeister). Rosenbloom(*e*) has found larger quantities in human bile while Rothschild and Felsen state that 0.08 per cent is the normal concentration.

Rothschild observed that the cholesterol content of the ingested food had an influence on the cholesterol concentration in the blood and bile.

Feeding cholesterol to dogs does not increase the cholesterol content of their blood because it is excreted so rapidly in the bile. Bacmeister and his pupils found that feeding proteins and fats increases the cholesterol content of the bile. They also found that in diabetes the hypercholesterolemia was usually associated with an increase of cholesterol in the bile. In pregnancy the cholesterol in the bile decreases along with an increase of the cholesterol in the blood. These facts indicate that the liver regulates the cholesterol content of the blood. Poisons which destroy red blood cells increase the amount of cholesterol in the bile. The solubility of cholesterol in bile is probably due to the presence of bile salts with which it forms a soluble compound (Wieland).

Fat.—Gall bladder bile contains an average amount of 8.3 grams of fat per liter. In fatty liver, the fat content of the bile may rise to 20 parts per mille.

Mineral Substances.—Besides sodium with which the bile acids are united, sodium and potassium chlorid, calcium and magnesium phosphates and iron are found in bile; of the last, there is about 40 to 115 mgs. per liter.

Tests of Liver Function

Owing to its size, it is possible for the liver to carry on its functions even when extensively diseased. It is only in diffuse lesions that disturbances of function occur. A liver riddled with tumors may carry on its

normal functions, while another, the seat of mild parenchymatous degeneration, may show evidence of disturbed function. In fact, it is probable that functional disturbances occur in the absence of gross or microscopic changes. A consideration of the literature teaches that it is well to know the state of several functions of the liver before arriving at a conclusion regarding the presence or absence of disease.

The levulose and galactose tolerance tests were first used by Strauss(*f*) and Bauer(*a*), respectively. 100 grams of levulose or 40 grams of galactose are administered in the morning before breakfast. Following the ingestion of these carbohydrates, a normal person will usually excrete little or no levulose and less than 3 grams of galactose. In the event of liver insufficiency, a considerable quantity of sugar may be excreted. As far as the writer knows, no one has studied the blood sugar curves after the ingestion of these carbohydrates, though it is apparent that helpful information might be obtained by this means.

The urea, ammonia and amino acid fractions of the urine and blood have been studied in diseases and in experimental lesions of the liver. In quite a few instances the methods have been inadequate and in others the results are open to criticism for one reason or another. The accurate gasometric determination of amino nitrogen was employed by Levene and Van Slyke in their study of the urine of animals poisoned with phosphorus and chloroform. No increase of amino nitrogen was observed even when the liver was extensively degenerated. In two cases of human cirrhosis, the amino acids of the urine were not increased.

In the toxemia of pregnancy, a condition often associated with necrosis of the liver, Losee and Van Slyke failed to find an increase of amino acids in the blood or urine though the urea nitrogen in the latter was diminished.

At the present time it appears that, with the possible exception of acute yellow atrophy, an increase of amino acids in the blood or urine is an infrequent occurrence in hepatic disease.

The behavior of the ethereal sulphate excretion before and after the administration of a known amount of one of the phenols has also been used as a test of liver function. Certain factors detract from the value of this test. It is known that some of the phenol may be oxidized or combined with glycuronic acid and that other organs besides the liver may conjugate phenols with sulphuric acid.

Whipple(*b*) and others have found that the concentration of fibrinogen in the blood is diminished in experimental lesions and diseases of the liver. In some cases no fibrinogen at all was found.

Goodpasture(*a*) has noted that the clotted blood of patients suffering from liver disease may liquefy in the course of 4 hours. Normal clotted blood remains unchanged for several days. This phenomenon is apparently due to the presence of a proteolytic ferment.

The blood lipase is increased in certain cases of liver disease.

In the absence of pernicious anemia or hemolytic jaundice, the presence of increased amounts of urobilin and urobilinogen in the urine is said to be a delicate index of disturbed liver function. The chemistry and clinical significance of these substances have been discussed in a previous chapter.

During latter years, Rowntree and collaborators have studied the rate of excretion of tetrachlorphthalein in liver disease. This dye is normally excreted in the bile. About 0.4 gram are administered intravenously and the amount contained in the 48-hour quantity of stool is determined. A normal person eliminates about 30 to 52 per cent of the dye within this time. A diminished excretion of the dye or its appearance in the urine is said to be indicative of liver disease.

Owing to the unsatisfactory state of our knowledge it is safe to say that considerable work remains to be done before the value of the various functional tests will be definitely established.

Pathochemistry of the Liver

The Liver Functional Tests in Disease.—The opinions of observers regarding the value of any one functional test vary considerably and are often contradictory.

Jacobson has recently shown that in Eck fistula dogs the tolerance for levulose is diminished while that for glucose is normal. The following table gives the results of the levulose test in various hepatic disorders (Strauss(*f*)):

Disease	Number of Observations	Percentage of Positive Results
Cirrhosis	127	83
Congestion	41	17
Catarrhal jaundice	27	70
Syphilis	12	75
Obstruction of common bile duct	32	62

A positive result was obtained in 15 per cent of patients not suffering from apparent disease of the liver. Churchman likewise obtained positive results in 23 per cent of 38 cases not suffering from liver disease. Rowntree, Hurwitz and Bloomfield found that of 534 levulose tests collected from the literature, 70 per cent of the patients with liver disease gave positive results, while 15 per cent of the patients not suffering from liver disease also gave positive results. Falk and Saxl(*a*) obtained positive levulose tests in 90 per cent of the patients afflicted with one of the follow-

ing disorders: Phosphorus poisoning, alcoholism, chloroform poisoning, parenchymatous degeneration of the liver, jaundice and cirrhosis.

Certain observers failed to confirm the value of the test (Shirokauer (*b*); Chesney, Marshall and Rowntree; Bloomfield and Hurwitz).

Bauer(*d*), who first suggested galactose, found a diminished tolerance for this sugar in all cases of catarrhal jaundice. Draudt obtained a positive galactose test in Eck fistula dogs and Roubitschek in dogs poisoned with phosphorus. Wagner confirmed Bauer's results in catarrhal jaundice.

Summarizing, one may say that while the results of the carbohydrate tolerance tests are to be cautiously interpreted, nevertheless a positive outcome has a certain confirmatory value. As previously stated, blood sugar determinations following the administration of these sugars will bring forth additional information which may enhance the value of these tests.

The administration of amino acids to patients suffering from liver disease is followed by an increased excretion of amino nitrogen in the urine (Jastrowitz; Masuda; Glaessner; Falk and Saxl). Frey observed an increase in amino acid excretion in cirrhosis and in animals poisoned with phosphorus or in whom the common bile duct had been tied, but found no change in the urea or ammonia excretion. The absence of fibrinogen in the serum has been observed in diseases of the liver and in animals poisoned with phosphorus and chloroform (Marshall and Rowntree; Whipple). The lack of fibrinogen may prevent coagulation of the blood (Doyon and pupils). Goodpasture noted autodigestion of the blood clot in 4 cases of cirrhosis confirmed by autopsy.

Whipple(*a*) noted an increase in the blood lipase in various liver diseases.

The rate of excretion of phenoltetrachlorphthalein in experimental lesions of the liver was determined by Whipple, Mason and Peightal, who emphasize the reliability of the test. Rowntree and assistants found that the dye was excreted in diminished amount in cirrhosis, carcinoma and in extreme congestion of the liver.

Marshall and Rowntree record the following observations on dogs poisoned with phosphorus and chloroform. An increase in blood lipase, a decrease in fibrinogen and a decrease in phthalein excretion. In phosphorus poisoning an increase of non-protein nitrogen, urea and amino-nitrogen in the blood. In chloroform poisoning the tolerance for levulose and galactose was decreased. An increased excretion of amino-nitrogen was observed in both conditions.

Jaundice.—The presence of bile in the blood and tissues and its absence from the intestine produces the condition called jaundice.

In incipient or slight jaundice bilirubin may be present in the blood serum before it appears in the urine or before it has stained the skin and mucous membranes. It is probable that bilirubin is combined with the

protein in the blood for, as Hoover and Blankenhorn have shown, it is not dialyzable until it can be excreted by the kidneys. In pernicious anemia and lead poisoning these observers have found bile salts in the blood, in the absence of bile pigments.

In severe and long standing jaundice, especially that due to gall stones, a retention of cholesterol in the blood may result, probably because it is not excreted in the bile. However, Rothschild and Felsen record low blood cholesterol values in severe jaundice complicating cirrhosis; therefore, the above simple explanation does not suffice. These authors suggest that a selective retention of bile pigments may occur while cholesterol is being eliminated in normal or increased amounts. The constitutional symptoms observed in severe jaundice, especially the slow pulse and the low blood pressure, have been variously ascribed to the action of bile salts and pigments respectively. King and Stewart have observed that the amount of pigment in a lethal dose of bile is sufficient to produce a fall in blood pressure and a slowing of the pulse, whereas the bile salts therein were without effect. When bilirubin was combined with calcium it became ineffective. They conclude that the poisonous effect of bile is due to the withdrawal of active calcium from the blood by bilirubin (King, Bigelow and Pearce).

Recently Wieland, working with pure salts of cholic and desoxycholic acids, was able to show that the salts of the latter, when perfused through the isolated frog heart, produce a diminution of ventricular contraction and an irregularity of the heart beat even in dilutions of 1:12,800. They also decrease the efficiency of striped muscle and hemolyze red blood cells. When desoxycholic acid was administered subcutaneously, this action on the heart, striped muscle and red blood cells was very much decreased. The salts of desoxycholic acid are not as powerfully hemolytic as sodium oleate, for the latter is active in a dilution of 1:50,000, while desoxycholic loses its activity in dilutions greater than 1:1,960 and cholic acid in dilutions greater than 1:220. The absence of bile salts results in a diminished absorption of fats from the intestine. The emaciation often observed in jaundice is probably to be ascribed to the withdrawal of fats from the dietary. The amount of urobilinogen and urobilin in the stool indicates whether the obstruction is complete or partial. The light color of the stools of jaundiced patients is due to the absence of urobilin and in some instances to the presence of increased quantities of fat.

In catarrhal jaundice, the liver parenchyma is usually affected as shown by the galactose test and the presence of urobilin in the urine, whereas, in occlusion of the common bile duct by tumors, or in experimental ligation of the duct, there is no indication of malfunction of the liver. The absence of glycogen from the liver in jaundice has frequently been observed. A decreased formation of urea does not occur.

Acute Yellow Atrophy.—Acute yellow atrophy may be a sequel of

catarrhal jaundice or any influence which tends to damage the liver cells. It is assumed that in this condition the parenchyma is sufficiently impaired by a toxic substance to permit autodigestion by the intracellular ferments (Fischler; Wells(*b*)).

The changes encountered in this condition have been accurately determined and clearly described by Van Slyke and Stadie. These authors examined the blood and urine during life and the composition of the liver after death. The amino-nitrogen of the blood was found to be increased to 14 to 26 mgs., that is about 2 to 3 times the normal, while the urine contained a large amount of ammonia and amino-nitrogen, but was low in urea. The liver had evidently lost part of its ability to deaminize amino acids and to convert ammonia into urea. The urea accounted for about 50 per cent of the total nitrogen, the ammonia for about 15 per cent, and the amino-nitrogen for about 11 per cent. (The normal percentage of amino-nitrogen in the urine is 2 per cent.) Although the liver was completely degenerated, urea formation still occurred. In the two days before death, there was an increase in acid excretion and on the day before death the plasma bicarbonate fell below the normal. This was due to the production of acids; whether the aromatic and lactic acids described by Roehmann were responsible for the acidosis was not ascertained.

The Composition of the Liver in Acute Yellow Atrophy

(Van Slyke and Stadie)

Water	71.0	per cent
Fat	13.5	per cent
Total solids other than fat.	14.9	per cent
Amino-nitrogen	0.134	per cent
Peptide nitrogen	0.072	per cent
Urea nitrogen	0.0043	per cent
Ammonia nitrogen	0.034	per cent
Creatinin nitrogen	0.0033	per cent
Creatin nitrogen	0.0143	per cent

The water content was considerably lower than that of the normal liver, and very much less than has been found in acute yellow atrophy by previous authors. The fat content was unusually high. Previous authors have usually found no increase of the fat content of the liver in this condition. The normal fat content of the liver is about 3 per cent. The remarkably low urea and the high ammonia content is to be ascribed to the diminished ability of the liver to synthesize urea from ammonia.

The increased excretion of amino acids in acute yellow atrophy has been known since the time of Frerichs (1861), who first found leucin and tyrosin in the urine in this condition. Wells also found a large quantity of free amino acids in the liver of acute yellow atrophy.

The changes which occur in the liver in phosphorus poisoning are very similar to those seen in acute yellow atrophy. In phosphorus poisoning, aromatic acids and lactic acid have also been found in the urine.

Van Slyke and Stadie believe that unaltered amino acids in relatively large quantities are found in the urine only when the liver is profoundly involved as is the case in acute yellow atrophy.

Cholelithiasis.—According to Bacmeister, 10 per cent of all human beings carry gall stones. Women are particularly predisposed, for they are likely to suffer from stasis of bile in the gall bladder due to pregnancy and the wearing of corsets. Pregnancy is associated with hypercholesterolemia and a diminished amount of cholesterol in the bile. At its termination, the cholesterol decreases in the blood and increases in the bile, and it is possible that crystallization in the gall bladder occurs at this time. Hypercholesterolemia occasionally occurs in cholelithiasis, even in the absence of jaundice.

The work of Aschoff and Bacmeister has shown that gall stones may develop in a perfectly aseptic gall bladder provided that the outflow of bile is interfered with. Under these circumstances, a solitary calculus may develop consisting almost entirely of cholesterol and presenting a radiate crystalline appearance when cut and polished. The presence of the calculus predisposes to infection, and the bacteria and the calcium rich mucus which is secreted favor the formation of additional stones. The stones which are found in infected gall bladders usually consist of bilirubin combined with calcium and cholesterol. The crystallization of cholesterol is known to occur in aseptic bile in vitro, especially when epithelial cells are present.

Another condition which may favor the crystallization of cholesterol is a diminution of the concentration of the bile acids which are known to form soluble compounds with this substance. A study of the bile from this angle might furnish additional information regarding the mechanism of gall stone formation.

Disturbances of Metabolism Accompanying Pancreatic Disease . . . . . *Burrill B. Crohn*

Physiological Considerations—Experimental Evidence of Disturbances in Metabolism, Resulting from Damage to the Parenchyma of the Gland or to Obstruction of Its Excretory Duct System—Disturbances in Human Metabolism Resulting from Diseases of the Pancreas or Obstruction of Its Ducts—Malignant Tumors of the Pancreas—Achylia Pancreatica, Hypochylia Pancreatica; Pancreatic Insufficiency—The Theory of an Internal Secretion of the Pancreas that Controls Food Absorption—The Signs of Disease of the Pancreas—Clinical Occurrence of Steatorrhea and Creatorrhea—The Functional Composition of the Fecal in Pancreatic Disease—Pancreatic Infantilism—Opotherapy in Pancreatic Disease—Prognosis of Pancreatic Disease—The Phenomenon of Acute Toxic Necrosis of the Pancreas—"Fat Necrosis"—The Toxic Element in Pancreatic Necrosis.

Disturbances of Metabolism Accompanying Pancreatic Disease[1]

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NEW YORK

Physiological Considerations

The pancreas, the "salivary gland of the abdomen," is a compound racemose gland that spans the face of the vertebral column in the upper abdominal quadrants. It lies deeply buried in the depths of the ventral cavity, in a position which had been almost inaccessible both to experimental physiologists and to clinical surgeons. It is only in recent years that more complete appreciation of its vital importance and protean functions has come to realization, and this only as a result of the brilliant physiological researches of Claude Bernard, Pawlow, Minkowski, and others, and of clinical observations of Fles, Senn, Fitz(*c*), Opie(*d*), and a host of subsequent workers.

Generally speaking we recognize two independent secreting functions of this gland, one an excretory or external secretion, an alkaline liquid containing, among others, the vital digestive ferments trypsinogen, steapsin and amylase; and an internal secretion which we have learned has a close relationship with the control of carbohydrate metabolism as well as a participating function in the endocrin control of body processes and the vegetative nervous system.

The pancreas secretes into the duodenum a fluid computed by Shumm (*a*), and by Glaessner(*a*), to amount to 300-600 c.c. a day. This fluid contains the inactive ferment trypsinogen which is activated into trypsin in the intestinal tract by enterokinase. Trypsin is a powerful proteolytic ferment which furthers the digestion of proteids begun in the stomach and carries the process to the amino-acid stage. There are also to be found in the external secretion of the acini of the pancreas an amylolytic ferment which completes the hydrolysis of starches and the inversion of sugars; and

[1] It is proposed in this chapter to deal only with such disturbances of metabolism as accompany diseases of the pancreas and affect its external secretion. The results of aberrations of the internal secretory functions of the pancreas are considered elsewhere in this system.

a lipolytic ferment (steapsin) which splits fats into fatty acids and glycerin.

It is thus seen that the acinar cells of the pancreatic parenchyma furnish the three main ferments which are of the greatest physiological and metabolic importance in the digestion of foodstuffs.

Diseases that affect or originate in the pancreas interfere with its function in two ways. The disease process either blocks the excretory ducts of the pancreas so as to prevent its important secretion from reaching the intestinal tract, or it acts by destroying the parenchyma of the gland proper. The net result in either case is approximately the same, that is, the glandular secretion that reaches the intestine is either markedly diminished or completely absent. The natural inference is that the preparation and digestion of the three main classes of foodstuffs is materially interfered with or suspended, resulting in diminished absorption on the part of the intestinal lacteals and epithelial cells, and a greatly increased excretion of undigested food elements in the feces. In well defined and advanced clinical cases such changes in absorption and excretion are often readily demonstrated; unfortunately for the simplicity and comprehensibility of the subject, it has been shown by numerous observers that such disturbances are not bound to follow even the complete blockage of the duct system or the destruction of by far a major portion of the secreting parenchyma of the gland. A mass of evidence, experimentally produced or obtained by careful clinical observation, has thrown much light on the subject and clarified many points hitherto in dispute, yet has left some of the vital points still unexplained and far from solution.

Experimental Evidence of Disturbances in Metabolism, resulting from damage to the parenchyma of the gland or to obstruction of its excretory duct system.—The experimental work that antedated the middle of the last century was in great part nullified by the lack of acquaintance of the workers with the details of the anatomy of the duct system in the animals operated upon (dogs).

To Claude Bernard, in 1856, is credited the accomplishment of writing the introductory chapters to our knowledge of pancreatic lesions, experimentally produced. His earliest experiments consisted in injecting into the duct system of the dog's pancreas irritating substances such as bile and fatty acids, or blockage of the ducts by the injection of paraffin. He was able to demonstrate a distinct disturbance in fat absorption and metabolism; his animals developed fatty stools, showed increased appetite but lost weight rapidly. The urine was not examined. The destruction of the pancreas in his animals was usually complete.

Abelmann attempted to perform total pancreatectomy upon dogs. The result observed was a complete failure on the part of the intestinal tract to absorb fat; nitrogen absorption varied between 30 and 80 per cent; a better absorption was demonstrable when the fat was administered in

emulsified form, such as milk. After partial extirpation of the gland, absorption was much better (fat 31.5 per cent, emulsified fat (milk) up to 80 per cent).

Abelmann contributed one further important fact, namely, that fat splitting even in totally depancreatized animals had not materially been interfered with; split fats ranged as high as 30-85 per cent.

Minkowski, and von Mering and Minkowski (*a*), performed an interesting series of experiments upon total extirpation of the pancreas. When all but a fraction of the tail of the pancreas had been removed, fatty stools appeared but no other disturbance was noted. When, at subsequent operation, the atrophic remnant of the tail was extirpated, a severe diabetes resulted. Thus was established the important relationship between the pancreas and carbohydrate metabolism. The disturbance was credited by these authors to the removal of an "internal secretion" of the pancreas.

Further experimental evidence on the effects of partial extirpation followed. Sandmeyer extirpated all except the tail of the gland; nitrogen absorption remained good, but fat absorption was materially interfered with, in some cases falling to zero in others remaining as high as 30-78 per cent. Harley repeated these experiments with very similar results; considerable loss of fat and nitrogen was shown to follow partial pancreatectomy.

Hedon and Ville found that after total pancreatectomy a dog absorbed only 18 per cent of lard or oil. In all cases the splitting of fat was well maintained.

Instead of extirpating the pancreas Rosenberg ligated completely all the ducts, arteries, veins, leading to the pancreas, thus causing complete blockage to the exit of ferments, as well as a consequent atrophy of the gland. Under these circumstances absorption of food elements remained nearly normal (90 per cent). He thus established the theory that the persistence of the gland in the body, though atrophic and though separated from the intestine, preserved digestive absorption. He attributed this, however, to the fact that ferments were absorbed vicariously into the circulation and reëxcreted by the intestinal mucosa, a supposition which is nowhere substantiated by later facts.

The findings of Zunz and Mayer convincingly showed that though in dogs the pancreatic ducts were firmly ligated and an atrophy of the pancreas produced, yet little of digestive disturbance ensued. If the atrophied remnant of pancreas was removed, food absorption suffered materially. As Minkowski and von Mering had done, these authors concluded that an internal secretory function of the pancreas controlled absorption.

Thus far we have noted two general conclusions:—First, that total destruction or total removal of the gland leads to marked disturbance in the intestinal absorption of fat and nitrogen as well as of carbohydrate metabolism; second, that separation or ligation of the ducts even though

secondary atrophy of the gland follow, does not necessarily create a sequential disturbance in absorption.

Lombroso(*a*), an Italian physiologist, offered some further valuable evidence. After either simple tying off of the ducts, or after production of an external pancreatic fistula (Pawlow) absorption of fats in dogs remains normal (55.9 per cent to 84.3 per cent). If the atrophied remnant of pancreas be now removed, fat excretion mounted rapidly to 40.4 per cent, 99.7 per cent and 113.5 per cent!

In another series of experiments Lombroso attempted to prove that a fraction of the pancreas transplanted vicariously under the skin could preserve good intestinal absorption. With the transplant viable and excreting outwardly, absorption was only fairly well maintained, varying between 46 per cent and 77.4 per cent. Whenever the graft was well preserved, absorption remained good. Upon removal of this transplant, the excretion of fat in the stool rapidly increased to 96.6 per cent and 97.8 per cent; nitrogen excretion varied similarly though not to so great a degree.

Pflüger directed criticism against these experiments in so far as he pointed out that the persistence of good absorption in the presence of a transplant could be due to vicarious excretion of digestive ferments into the intestinal tract.

Lombroso's contention was that it was an internal secretory function of the gland and not the external secretion that maintained digestive efficiency. (Compare von Mering and Minkowski(*a*) and Zunz and Mayer.)

To establish this point he studied metabolism in a dog with an external pancreatic (Pawlow) fistula, allowing the dog at times to lick the escaping secretion, at other times muzzling the dog. No differences were seen in comparing the two periods.

Lombroso's experiments provoked much criticism. Hess(*b*) and also Sinn pointed out that Lombroso had probably failed to tie all the ducts of the dog and that in this way the partially preserved absorption was to be accounted for. In one dog in which Hess(*b*) carefully tied all the ducts, he noted a loss of 45.4 per cent nitrogen and 95.3 per cent of the ingested fat. Lombroso's answer was that by his technic Hess had probably destroyed the gland as well as tied the ducts.

Burkhardt repeated Lombroso's experiments in an identical manner and seemed to show that if the dog licked the secretion of the fistula intestinal absorption was retained at a high level; not so when the fistula fluid drained away.

To answer these criticisms Lombroso again repeated his experiments and substantiated all the statements he had previously published. Lombroso(*b*) further showed that not even by feeding to the dog large amounts of duodenal contents from other healthy animals could he increase fat and nitrogen absorption in his depancreatized dogs.

Fleckseder, the same year, published a complete substantiation of Lom-

broso's fistula experiments, both with licking and without licking of the escaping fistula fluid.

Niemann and also Brugsch(*d*) offered evidence in favor of Lombroso's claims. Both these workers found absorption of fat and nitrogen practically normal when all the ducts were securely tied. They both proved that they had tied all the ducts, for at autopsy on their dogs no trace of tryptic ferment was found in the duodenal juices. If, on the other hand, the vessels to the pancreas were tied, causing atrophy and destruction of the gland, fat absorption fell to 39.6 per cent and nitrogen to 62 per cent.[2]

Jansen's experiments, which were a duplication of much of Lombroso's work, upholds the statements made by the latter. With a subcutaneous graft as the sole representative of pancreatic tissue in the body, absorption of fat was fairly well maintained varying between 67.4 per cent and 75 per cent. After extirpation of the graft, absorption of fat fell to 24.6 per cent. On a strict protein diet, more fat was excreted than actually ingested.

Convincing as these experiments and their corroboration by independent workers seem to be, the matter was not to end here. For Visentini demonstrated that pancreatic ducts, when ligated and cut, rapidly reëstablished their continuity with the intestinal lumen. Further he found that when the ducts were thoroughly separated without removal of the pancreas, that fat absorption fell to between 20 per cent and 40 per cent. He thus revives the theory that it is an essential necessity for absorption that the external pancreatic secretion reach the intestine.

More recently, valuable work in this country has contributed some important findings. Pratt, Lamson and Marks found a serious disturbance after ablation of the ducts and insertion of omentum between the cut ends; nitrogen loss rose to 77.8 per cent, fat loss to 88.7 to 95.2 per cent.

Benedict and Pratt feeding only meat to dogs with the ducts ligated found a nitrogen loss of 32.1 to 57.7 per cent. The feeding of fresh pancreas gland seemed to increase absorption.

In both these latter groups of experiments it can be held that a progressive atrophy and degeneration of the gland accounted for the poor absorption. This was the same argument with which Lombroso retaliated against his critics. In fact, Pratt and Spooner themselves point out that an extensive injury results to the pancreas as a result of the extensive ligation. This, they contend, is shown by the rapidly reduced ability to assimilate glucose shown by their dogs.

It would seem to the author that not sufficient recognition has been given the fact that after ligation of the ducts of the pancreas alone, serious injury to the parenchyma of the gland may result. It will be seen in the discussion under the experimental production of acute pancreatitis

[2] The normal absorption for the dog is, nitrogen 98 per cent, fat 96 per cent, but in all cases approximately 90 per cent or over. (Burkhardt.)

that one of the most successful means for producing experimentally pancreatic necrosis and degeneration, as also creating fat necrosis, was by this very method, namely, tying off of the ducts. Not only the exclusion of the pancreatic secretion from the intestine is thus carried out, but a veritable decomposition, hemorrhage and necrosis of the gland results in a large percentage of cases. If the animal survives the procedure and its resultant effects on the gland, the least after-effect is a chronic productive obliterating pancreatitis or an atrophy of the gland.

See the experiments of Hildebrand and of Dettmer in Part II of this article, on the experimental production of fat necrosis in animals.

Finally, we may bring into evidence the results obtained by McClure, Vincent and Pratt. In a series of four dogs, they removed entirely the processus lienalis and the corpus pancreatis and formed of the remaining processus uncinatus a subcutaneous graft. In a fifth dog the processus uncinatus was allowed to remain in the abdomen though completely cut off from the intestinal wall. The mean average of fat absorption in the four animals was 50.19 per cent, a figure which is considerably better than that reported by Pratt, Lamson and Marks who caused an atrophy of the gland by ablation of the ducts and the insertion of omentum between the cut ends. Thus it would seem that the preservation of a viable graft helps to maintain absorption metabolism. In dog 4 of the series of experiments by McClure, Vincent and Pratt, the main duct of the processus uncinatus was saved with the graft and brought out upon the surface of the body so that abundant pancreatic juice was continually escaping and no utilization of the external secretion was possible. Yet the dog absorbed 74.3 per cent of the ingested fat. Upon muzzling the dog it was shown that the amount of fat actually absorbed per kilo was sustained. In two of the dogs in this series a more marked deficit was shown, absorption amounting only to 27.37 per cent and 23.9 per cent.

At a secondary operation, these authors removed the subcutaneous pancreatic graft from the animals. Fat absorption subsequent to this total pancreatectomy fell to between 17.59 per cent and 45.3 per cent, averaging now only 31.8 per cent. It is remarked that this is not an inconsiderable amount of fat for an animal completely lacking in pancreas to absorb.

It is difficult to harmonize the various findings of the many investigators who have undertaken to clarify this problem. On the other hand it is difficult to escape from the following conclusions:

1. Normally, the external secretion of the pancreas is an important agency in the digestion and the absorption of fat and nitrogen.

2. Exclusion of pancreatic juice from the intestine of dogs causes a prompt, though moderate drop in absorption of food products.

3. Total extirpation of all pancreatic tissue causes very severe loss in absorption power (as well as diabetes), though some persistence of absorption of fat and nitrogen is seen.

4. The preservation of a viable graft of pancreatic tissue anywhere in the body, though not connected with the intestinal lumen, serves materially to maintain and preserve absorption. This power is exercised in the nature of an internal secretion.

5. The degree of secondary atrophy of the pancreatic remnant determines the absorption power of the intestine.

Disturbances in Human Metabolism Resulting from Disease of the Pancreas or Obstruction of Its Ducts

We have seen in the preceding section, that one of the most difficult questions to answer during the experimental studies was the one that concerned the patency or non-patency of the pancreatic ducts after attempts at artificial production of a complete blockage of pancreatic secretion. This debatable question is carried down with us in a consideration of the metabolism disturbances accompanying human diseases of the gland and its duct system. The literature on the subject abounds with studies of metabolism in pancreatic disease, but always the question arises: "Was the pancreatic disease actively present when so reported clinically, and were the ducts actually blocked at the time when the experiment in metabolism was performed?" This ever recurring question brings into doubt many of the case reports found in the literature. Furthermore, unless an autopsy had been performed soon after the observations had been made, we remain in the dark regarding the state of functional activity of the gland parenchyma at the moment of the experiments.

A further complication is introduced when we consider that the close anatomical relationship between the common bile duct and the pancreatic duct, causes an obstructive jaundice to be a very common concomitant to the obstruction of the pancreatic duct. Obstructive jaundice gives rise to distinct metabolic disturbances, being itself mainly characterized by a diminished ability on the part of the intestine to emulsify and absorb the fats. In the careful studies of Friedrich Müller(*a*), it was noted that simple obstructive jaundice resulted in a diminution of the fat absorption, nitrogen absorption remaining approximately normal. In normal individuals Müller found the stool to consist of 22.7 per cent of fat; in simple icteric individuals the fat content of the stool rose to 49.1 per cent. Fat absorption in normal persons was found to be 91.1 per cent; in icterus only 45 per cent of the ingested fat was absorbed. Ad. Schmidt(*b*) found these figures rather high, and reports for simple icterus a fat loss of only 25.9 per cent of the ingested fats.

The arrangement of the main pancreatic duct and the existence in man of an accessory duct, the duct of Santorini, has often raised the question

whether in disease of the pancreas and blockage of the main duct, the accessory duct cannot take over its function and maintain in that way the permeability of the duct system. In the dissection of fifty cadavers, Claremont has shown that in 76 per cent of the cases the duct of Santorini is either failing anatomically or, when present, is functionally inactive and impervious. In 4 per cent of the cases, the Santorini duct was independent and pervious but drained only a small fragment of the gland. In most of the other cases, both main and accessory ducts were closely related and communicated the one with the other, so that a disease process that affected one would undoubtedly have affected the other. The actual autopsies in cases of diseases of the pancreas have practically always failed to find an active patent accessory duct taking over the function of the disabled main duct. Pratt(*b*) mentions one instance only wherein this was observed.

One meets in the literature metabolism studies on cases in which the diagnosis of pancreatic disease rests solely upon the basis of certain clinical tests or on the outcome of one or more of the various laboratory procedures for establishing such a diagnosis. Among the more important of these are the presence of an excess of neutral fat in the stool causing the classic picture of "fatty stools," and the presence of an abundance of undigested muscle fibers (creatorrhea).[3] Ad. Schmidt devised a test based upon the inability of the intestine in pancreatic disease to digest the nuclei of muscle tissue (beef-cube test); this test was modified by Kashiwado who utilized thymus gland and demonstrated in the feces the undigested and undissolved cells and nuclei. On a similar plan are the tests of Sahli who utilized a gelatin capsule containing iodoform, or salol, the capsule being dissolved supposedly only in the intestine and in the presence of pancreatic ferments (trypsin).

More recently attempts have been made to test directly for the presence of the pancreatic ferments in the stool, in the urine, the blood and in duodenal or stomach contents. An olive-oil breakfast was utilized by Volhard to induce regurgitation of duodenal contents into the stomach, the material extracted being examined for tryptic activity. The diastatic activity of the feces and of the urine were made the basis of a test introduced by Wolgemuth, and amplified and observed by Wijnhausen(*b*), Gross(*a*), T. R. Brown(*a*), and others. By this latter method, obstruction or disease of the pancreas is evidenced by an increased amylolytic activity in the feces. These latter methods of direct examination for pancreatic ferments, while promising much, have failed of being decisive or giving clear-cut indications of pancreatic disease.

Of late it has become possible to obtain directly the contents of the duodenum by means of a specially devised tube (Einhorn(*a*), Gross(*b*), Hemmeter), and thus to test for the presence or absence of pancreatic

[3] These phenomena will be separately considered in a later section.

ferments, or for functional variations in the strength of the pancreatic secretion so obtained. It has been shown that normal human pancreatic ferments as obtained from the duodenum have a constant value (Crohn(*a*), Einhorn and Rosenbloom, McClure), and that in diseased conditions of the pancreas affecting any of its ducts these ferments either are absent or definitely diminished (Hess(*c*), Chace and Myers(*a*), Bondi and Solomon, Einhorn(*c*), Crohn(*b*)), etc. The latter or duodenal method, being the most direct, lending itself to the more exact chemical studies, bids fair to replace most of the older and more indirect methods for demonstration of the presence of the active ferments of the gland in the intestinal tract.

Objections can be found to most of the tests as practiced, and in the older ones, the clinical application of the tests has failed to substantiate the claims made for them by their originators.

There are, however, reported in the literature many cases of verified pancreatic disease in which exact clinical data regarding metabolism and food absorption have been obtained, and in which at autopsy or operation the exact status of the pancreas has been ascertained. It is on the basis of these data that there has been accumulated a composite picture of the disturbances in metabolism that accompany pancreatic disease.

As a clinical observation, disturbances of fat metabolism were first observed by Kuntzmann, and independently by Richard Bright. The picture of the typical "fatty stool" pathognomonic of pancreatic disease was clearly described by the latter; many years later Fles made his remarkable observation on the large amount of muscle fiber remaining in the feces of patients suffering from pancreatic disease (creatorrhea). Clinical observations in the next decade were numerous but threw no more exact light on the phenomenon. Stimulated, however, by the careful animal experiments of von Mering and Minkowski(*a*), Abelmann, Sandmeyer, and others, accurate chemical data began to accumulate after 1895; since that time there has been an increasing number of careful chemical studies on human digestion and absorption in pancreatic disease.

Friedrich Müller(*a*) noted three cases in which complete obstruction of the pancreatic duct occurred. The percentage of fat content in the feces was 28 per cent, 29.5 and 44 per cent; normal about 14-26 per cent (von Oefele). Müller attributed the large loss of fat more to the associated jaundice than to the closure of the pancreatic duct.

Deucher in a case of carcinoma of the pancreas with closed duct of Wirsung and only slight compression of the bile duct, found a fat absorption of only 17 per cent and a nitrogen absorption of 70 per cent.

In a second case of carcinoma, the obstructive jaundice had been relieved by a cholecystoduodenostomy, thus eliminating the icterus as a disturbing factor. The percentages of absorption were, fat 47.4 per cent,

nitrogen 81 per cent. Fats were split in all cases to the extent of 60-80 per cent.

Weintraud, in a case of pancreatic cirrhosis verified at autopsy, found a fat absorption of 78 per cent and a nitrogen absorption of 55 per cent; there was considerable interference with fat splitting, 72-76 per cent being neutral fat. Glaessner and Sigel in a case of chronic pancreatitis found fat absorption reduced to 43.9 per cent, nitrogen absorption 58.5 per cent.

The observations of Brugsch are important. He found:

	Fat Abs.	N Abs.
Carcinoma of pancreas with obstructive jaundice	15 per cent	61 per cent
Abscess of pancreas-jaundice absent	40.3	79.
Carcinoma of pancreas-jaundice absent	38.	80.
Closure pancreatic duct-jaundice absent	30.	74.6

In four cases of closure of bile duct alone (stone, etc.), without participation of the pancreas in any way, Brugsch estimated a control figure of 55 per cent for fat absorption and 92 per cent for nitrogen absorption in icterus. Brugsch regards any figure for fat absorption of less than 40 per cent as due to a diseased pancreas.

In a case of subacute pancreatitis, Brugsch and Koenig found fat absorption varying from 27.8 to 40.3 per cent; a few weeks later, when much improved in health, the patient was able to absorb 73.9 per cent of the ingested fat.

Ernst Meyer, in a case of carcinoma of the pancreas with obstructive jaundice, found nitrogen absorption reduced to 34-41 per cent, fat absorption reduced to 38 per cent.

The experience of Gigon is instructive, for in a case with pancreatic cirrhosis nitrogen absorption was 57 per cent, fat 79.5 per cent. He concluded that pancreatic disease did not materially interfere with food absorption. The exact status of the gland and the question of the patency of the ducts must however remain unsettled in such a case.

Wijnhausen(*a*) contributes the first metabolism study in which the ferments of pancreas were investigated. He determined in a case of carcinoma of the pancreas that both trypsin and amylase were markedly diminished, indicating an obstruction of the ducts. Under these conditions he found fat absorption only 26.4 per cent, nitrogen absorption 67.1 per cent.

Ehrmann observed a case of pancreatic cirrhosis with closure of the pancreatic ducts, in which the jaundice had been relieved by a cholecystoenterostomy. The stools were characteristic of pancreatic disease, that is, they contained a large excess of muscle fibers and were fatty and typically oily in appearance. Mathematically expressed, there was a loss of 42.8

per cent of nitrogen and 50.16 per cent of fat, a marked increase over the normal. The splitting of the fats was not affected.

The results so far tabulated record all positive interference with absorption as a result of disease or obstruction of the ducts. The following case of Keuthe seems to be a notable exception. His observations refer to a case of advanced atrophic pancreatitis resulting from numerous pancreatic calculi. The ducts were destroyed or blocked, as well as the parenchyma of the gland. The islands of Langerhans seemed well preserved. In this case the fat absorption was 91.2 per cent, splitting of neutral fats into fatty acid and soaps *above* normal. In spite of the fact that the clinical symptoms of pancreatitis were present, namely, diarrhea, weakness, emaciation and intermittent glycosuria, no deficiency in fat absorption was demonstrable.

This observation is more remarkable since the subject of the experiment is the same patient upon whom Glaessner and Sigel four years previously had studied metabolism. (See above.) At that time the latter had found marked interference with fat and nitrogen absorption.

Brugsch(*d*) who had contributed some exhaustive experiments on animals had also an opportunity to study the disturbances in human metabolism. He regards losses of fat up to 45 per cent and of nitrogen up to 11 per cent as attributable merely to closure of the common bile duct. Amounts above this figure he considers as due to pancreatic disease. Thus in a case of carcinoma of the pancreas (duct blocked) with absent ferments in stool and regurgitated stomach contents, he found a fat loss of 60 per cent and a nitrogen loss of 36 per cent. At autopsy the entire gland tissue was diseased.

Similarly in a case of Albu's in which the whole gland was replaced by scirrhus carcinoma, only 21 per cent of fat was absorbed; the stools were typically fatty and contained a large excess of undigested muscle fibers.

These last two reports are very instructive; in the first, there was a blockage of the duct and a pathological change of the parenchyma. In the second case (Albu) the destruction of the entire parenchyma is reflected in the enormous fat loss in the stool.

In a series of five authenticated cases (Tileston) in which both ducts were closed by carcinoma at the head of the pancreas fat absorption was distinctly impaired ranging between 24.4 per cent and 51.9 per cent; nitrogen absorption ranged between 38 per cent and 85.5 per cent. Blockage of the ducts, with the apparently necessitated atrophy of the glands, thus seems to produce a real disturbance in the absorption. Tileston is willing to accept a 50 per cent fat loss as attributable to the jaundice, but regards everything above this as a sequel of pancreatic disease.

Oskar Gross(*a*) studied carefully two cases of chronic pancreatitis, one of which, at autopsy, had pancreatic calculi and atrophy of the gland. Nitrogen absorption was 51 per cent, 68.9 per cent and 63.5 per cent; fat

absorption between 45 and 50 per cent in the first case, and over 70 to 73.8 per cent in the second case. This also in face of the fact that Gross forced huge amounts of fat in his test diets. Apparently, while some disturbance takes place, even in advanced chronic pancreatitis some functional ability to absorb food is always retained.

Ehrmann and Kruspe emphasize particularly the nitrogen loss in a case of chronic sclerosing pancreatitis with stricture of the duct of Wirsung. This loss amounted to over 34 per cent and corresponded to the marked diminution in trypsin in the intestinal tract. They refer all changes in fat and nitrogen absorption to the obstruction of the duct and deny the theory of the control of absorption by an internal secretion.

Pratt found a fat loss of 58.9 per cent in a case of chronic pancreatitis with obstruction of the ducts, and a fat loss of 79.9 per cent in a case of cancer of the pancreas with occlusion of the ducts. Pratt mentions one case of carcinoma wherein a patent accessory duct of the Santorini was found; here the fat loss was only 28.8 per cent.

In a most typical case of pancreatic insufficiency due to chronic pancreatitis Spriggs and Leigh observed oily defecations amounting in weight to the enormous figure of 1,000 to 2,649 grams. Fat excretion ranged between 55 and 99 per cent of the fat intake.

Crohn(*c*) found in a case of acute pancreatitis with entire destruction of the body and tail of the gland but preservation of a portion of the head, that fat absorption suffered but little, 91.6 per cent of the ingested fats being absorbed. In neither chronic pancreatitis nor carcinoma of the head of the pancreas were severe disturbance seen. In all of his cases, the pancreatic ferments were tested for in the fresh duodenal contents removed by duodenal tube; the ferments were uniformly either absent or only weakly present.

In discussing and critically reviewing this list of observations it is essential to again remind ourselves that in many of the cases no mention is made of the patency of the duct at the time of the metabolism study; that many cases were not observed at autopsy, the clinical diagnosis alone determining the nature of the malady. Even autopsy descriptions often fail to detail the condition of the gland, and microscopic studies are rare. Under these handicaps, it is generally agreed that conclusions are unsatisfactory and often confusing.

In order to facilitate a study of the data in the literature the cases published have been tabulated and are presented in tables 1, 2, 3, 4, and 5.

Thus arranged in groups one may attempt to draw certain conclusions.

In simple closure of the pancreatic duct (Table I) wherein it has been shown by ferment studies or by pathological examinations that the pancreatic secretion has been excluded from the bowel, we will note that fat losses vary from 19.7 per cent to as high as 73 per cent, and nitrogen loss from 25.4 per cent to 50.9 per cent. Thus there appears to be a defi-

TABLE I

FAT AND NITROGEN EXCRETION WITH CLOSED PANCREATIC DUCT

Author	Fat Excretion * Per Cent	Nitrogen Excretion * Per Cent
Brugsch	70.0	25.4
Harley—Inflammatory Stricture	73.0	40.0
Pratt	58.8	50.9
Delfino—Peripancreatic Cyst	19.7	

* Represents per cent of ingested fat and nitrogen which was excreted.

nite interference of absorption dependent upon pancreatic duct blockage. In the case of Harley wherein the block resulted from an inflammatory stricture due to a cicatrized duodenal ulcer the loss was high and absorption from the intestine relatively very poor. As there was no autopsy upon his case, the condition of the pancreas remains uncertain, a factor which should be known before a conclusion is drawn. This factor is better furnished in the report of Brugsch(*d*) who found in a carcinomatous obstruction of the duct a loss of 70 per cent fat and 25.4 per cent nitrogen; upon autopsy the entire gland was diseased, atrophic and replaced by carcinoma. Again, in the case of Delfino where the obstruction was due to a simple peripancreatic cyst with preserved gland parenchyma, the loss of fat is less than 20 per cent.

Evidently, simple obstruction is not the main factor in metabolism disturbance; a destruction of the secreting tubules is a necessary concomitant.

In acute pancreatitis (Table II) we see in the case of Brugsch and

TABLE II

FAT AND NITROGEN EXCRETION IN ACUTE PANCREATITIS

Author	Fat Excretion Per Cent	Nitrogen Excretion Per Cent
Umber and Brugsch—Abscess	59.7	
Brugsch and Koenig	59.0	
Crohn	9.4	

Koenig a loss of 59.7 per cent of the ingested fat during the critical part of the disease; this loss increases to 72.2 per cent before recovery, after clinical improvement and recovery the absorptive power is regained, up to 73.9 per cent for fat. As the intake of fat was scanty (only 49 grams per diem) the losses encountered are very considerable and indicate extensive damage to the gland (as was confirmed by finding a large abscess of the pancreas). The ability of the pancreas to recover its normal properties is shown by the improvement following the return to health.

In the case of Crohn(*c*), a case of severe pancreatitis with profound shock, fever, vomiting and prostration, fat absorptive tests at the height of

the disease showed an ability to absorb over 90 per cent of the fat ingested, though the intake here was 101 gms. or double that of the preceding case.

It is just such contradictory facts that make it so difficult to deduce conclusions.

TABLE III

Fat and Nitrogen Excretion in Chronic Pancreatitis

Author	Fat Excretion Per Cent	Nitrogen Excretion Per Cent
Weintraud	22.0	45.0
Hirschfeld—6 cases	29.4-47.2	30.4
Ehrmann	50.1	42.8
Glaessner and Sigel	56.1	41.5
Tileston	72.0	62.0
O. Gross	55.4	50.8
Ehrmann and Kruspe	33.3	34.0
Crohn	34.7	16.4
Crohn	5.6	6.0
Spriggs and Leigh	55-99	

Chronic pancreatitis—these were cases of simple primary cirrhosis of the pancreas or of interstitial pancreatitis secondary to neoplastic obstruction of the Wirsungian duct. The fat losses range from 5.6 per cent to 6.9 per cent, averaging again 39.8 per cent, a rather high figure for the latter. In most of these cases a complete atrophy of the gland is present. It would appear, however, that the mere presence of the gland in the body is a highly efficient means for preserving at least a fair degree of absorption. This fact is emphasized in the article by McClure, Vincent and Pratt who state: "After the complete removal of all pancreatic tissue from an animal, the absorption of considerable amounts of fat can still take place."

In a case of Crohn, there was present a primary intralobular cirrhosis of the pancreas: the ferments in the duodenal content were present very weakly. At autopsy, a primary connective tissue proliferation was seen invading the acini of the gland, destroying the secreting tubules and causing a cicatricial stenosis of both main pancreatic duct as well as of the common bile duct in its course through the head of the organ. No very considerable metabolism disturbance is seen; fat excretion is 34.7 per cent which in the face of the icterus is not exorbitant and nitrogen loss 16.4 per cent. Again, we conclude that it requires a very extensive destruction of the gland to produce the typical metabolism disturbances. Interstitial pancreatitis, the more common form, such as is secondary to cholelithiasis, syphilis, etc., does not apparently give rise to absorption disturbance.

Pancreatic Calculus and Its Sequel, Table IV.—Probably no single cause is more potent in producing an extensive cirrhosis of the gland than is pancreatic calculus; the stone or more usually stones occupy the main duct system, completely blocking the excretion of the pancreatic juice and

TABLE IV

FAT AND NITROGEN EXCRETION IN CALCULOUS CIRRHOSIS OF PANCREAS

Author	Fat Excretion Per Cent	Nitrogen Excretion Per Cent
Gigon	20.5	40.3
Keuthe	9.8	....
Barbour	....	44.2
O. Gross	26.2	31.0

setting up an extensive inflammatory reaction and atrophy. Fat losses in atrophy due to calculus average 18.8 per cent, nitrogen loss 39.4 per cent; proteid metabolism evidently suffers more than does fat digestion.

Malignant Tumors of the Pancreas

Under this heading are grouped, not cases in which merely the duct has been blocked by a small epitheliomatous new growth of the diverticulum or papilla of Vater, but cases in which the carcinoma has extensively invaded and destroyed secreting tubules.

In these cases we note the fat loss ranging between 28.2 per cent and 85 per cent, averaging 62.14 per cent; nitrogen loss is not so extensive, ranging between 11 per cent and 41 per cent, averaging 28.34 per cent.

TABLE V

FAT AND NITROGEN EXCRETION IN TUMORS OF THE PANCREAS

Author	Fat Excretion Per Cent	Nitrogen Excretion Per Cent
Deucher	83.0	30.0
Deucher—Cholecystenterostomy	52.6	19.0
Brugsch	85.0	39.0
Brugsch	64.0	20.0
E. Meyer	38.0	34-41
Wijnhausen	73.6	32.9
Brugsch—ducts closed	60.0	36.0
Albu—cancer and atrophy	79.0	.....
Tileston	75.6	19.8
Tileston	68.0	.....
Tileston	52.6	14.5
Tileston	45.6	21.1
Tileston	49.1	.....
Pratt	79.9	34.8
Crohn	28.2	11.0
Crohn	60.0	15.0

This is the first group of cases in which as a whole the loss of fat is consistently over 50 per cent, thus fulfilling the dictum of Brugsch(*d*) who required 50 per cent or more, and of Tileston who required a loss of 60 per cent or more as clearly indicating pancreatic disease. Apparently there are more "factors of safety" (Meltzer) in nitrogen than in fat

metabolism, for even in this extensive neoplastic destruction of the parenchyma of the gland protein metabolism does not suffer so extensively as does fat digestion.

That metabolism suffers in proportion to the incapacitation of the parenchyma is apparent in the observations of the author in a case previously reported (Crohn(*c*)) in which the diagnosis of carcinoma of the head of the pancreas was made by duodenal content analysis (total exclusion of bile and ferments). For several weeks no marked disturbance took place; but as later the new growth invaded and destroyed gradually the entire gland, typical fatty stools, and creatorrhea made their appearance. *The destruction of the gland was confirmed* by careful autopsy study. Friedrich Müller(*a*), whose absorptive experiments are the first known to us, described cases of complete absence of pancreatic juice from the bowel without fatty stools (steatorrhea). Franke found that after surgical removal of a carcinoma involving the head and body of the pancreas, no glycosuria or fatty stools were produced, apparently sufficient of the processus lienalis remaining to maintain metabolism balance. This remarkable surgical experiment confirms similar experimental procedures on dogs.

That there is no mechanism in the body that can take over the function of the gland is shown by the fact, pointed out by Allen(*a*), that Sandmeyer's dogs, with only atrophic remnants of gland remaining, gradually developed in the course of many months glycosuria and impaired food metabolism.

The carcinoma cases in human beings are analogous examples.

Friedrich Müller held that the poor absorption was due to poor digestion and preparation of the food in the intestine, as evidenced by diminished saponification; later observers have refuted this contention. Brugsch(*d*) experimentally demonstrated normal protein metabolism and amino-acid formation in dogs with ligated ducts; and numerous experimental and clinical observers have shown normal percentage of fat splitting and saponification in the intestines in pancreatic disease (Brugsch, Tileston, Pratt and others).

The claim of Bondi and Bondi that epithelial degeneration took place in the mucosa of the intestinal tract has found no confirmation and few believers. Nor will interference with intestinal and gastric motility account for the symptoms of disturbed nutritional equilibrium as suggested by Brugsch(*d*) and others.

Attempts have been made to explain the maintenance of food absorption in cases with duct obstruction, on the basis that absorption from the obstructed ducts of the stagnant though active ferments takes place, with re-excretion through the intestinal wall. Pflüger and Abelmann were the main exponents of this doctrine. Experimentally at least, when the ducts are tied, trypsin is absent from the intestine (Brugsch(*d*), Werzberg, Lom-

broso(*b*)). The same holds good for human cases in instances of pathological duct obstruction (Orlowski, Gross(*c*), Pratt(*b*), Tileston, Crohn (*b*), Matko and others).

Three main conclusions may be drawn from the reports in the literature regarding the metabolism of digestion and absorption in pancreatic disease.

1. The nature of the disease does not determine the degree of fat and nitrogen disturbance.

2. The amount of food absorption is independent of the patency of the duct, or the activity of the external secretion of the gland.

3. The degree of interference with intestinal absorption is dependent upon the extent of destruction of the parenchyma of the gland.

4. That by means of an internal secretion the pancreas controls absorption or at least complements the digestion and absorption capacity of its external secretion.

Conclusions 1 and 2 are based upon experimental as well as clinical evidence. The most difficult obstacle to overcome to its acceptance is the work of Pratt, Lamson and Marks and also Hess(*b*). Yet the former assert that a rapid and complete atrophy of the gland followed its separation from the intestine, and it is therefore more logical to attribute to this atrophy the disturbances that follow.

As regards conclusions 3 and 4, could one demonstrate a direct proportion between parenchyma disorganization and interference with absorption, the solution of the problem would be materially advanced. Such exceptions as could or would be advanced against this conclusion would be in the nature of citation of cases wherein normal or good absorption was maintained in the face of the destruction of almost all the gland. Such exceptional instances can be explained only on one basis, namely, that small remnants of parenchyma can and often do succeed in preventing metabolism imbalance. Not the amount alone, nor the size, of the surviving fraction of tissue, but its functional activity is the deciding factor, a point which is amply verified by the experiments of Lombroso(*a*), Fleckseder, Niemann and others, and clinically by the cases of Walker, Keuthe, O. Gross(*a*) and others.

Conversely, the phenomenon of emaciation and fatty and nitrogenous stools when a large amount of pancreatic tissue survives the disease, is again explainable only upon the functional inactivity of the surviving gland tissue. Thus to the above conclusion should be added a fifth, namely, that the degree of disturbance is proportional not alone to the extent of the damages to the parenchyma but also to the *functional ability of the surviving fragment to compensate for the loss.*

Achylia Pancreatica, Hypochylia Pancreatica; Pancreatic Insufficiency

Under these various titles have been described cases in which there exists a *functional* diminution of the external secretion of the pancreas. The clinical or pathological picture was first noted by Ad. Schmidt(*b*); in certain cases of achylia gastrica he attributed the accompanying diarrhea to pancreatic insufficiency. He studied four cases of achylia gastrica with loose diarrheal movements. The cases were put upon a test diet, known, and now generally employed for the detection of pancreatic disease under the name of the "Schmidt(*a*) Diet." [4] Upon this diet he observed diminished or absent trypsin in the stool, as well as a positive Schmidt nuclear test. Reasoning from this he takes the stand that the pancreas is at fault and is responsible for the diarrhea. In later years Schmidt(*b*) describes cases of achylia pancreatica independent of achylia gastrica and associated with steatorrhea.

Gross(*a*) is inclined to agree with Schmidt; while he found neither creatorrhea nor steatorrhea to be present, he did find diminution of trypsin by stool tests. The point is made by both Gross(*d*) and Matko that hydrochloric acid medicinally prescribed causes improvement in the diarrhea, and the loose conclusion is drawn that the improvement results as a sequel to the natural stimulation of pancreatic secretion by its physiological excitant, hydrochloric acid. Pratt(*b*) is inclined to deny achylia of the pancreas on the basis that steatorrhea and creatorrhea are absent in the achylia gastrica and are essential equivalents to the absence of the external secretion of the gland. Hypochylia pancreatica he suggests as a better name, indicating a partial rather than a total functional suppression of pancreatic juice.

To admit of the fact that pancreatic secretion varies in strength of ferments, in normal individuals or in those mildly sick with various complaints, would tend to invalidate much of the work upon which the diagnosis of pancreatic disease has been founded. Following the teaching of Rehfuss we are free to admit wide ranges of acidity for gastric secretion in normal individuals. The same range of alkalinity may possibly obtain for pancreatic secretion in normal humans, yet the exact chemical work of McClure seems convincing that under normal conditions the ferments of the pancreas are excreted in constant concentration (Crohn(*a*)). Matko speaks of conditions of hypochylia, achylia, hyperchylia pancreatica, etc., though his basis for such classifications is insufficient (stool tests for tryp-

[4] In studying pancreatic disease it is essential that a standard uniform diet be employed. For this purpose the diet proposed by Ad. Schmidt is generally accepted. It consists of 1.5 liters of milk, 100 gms. of zwieback, two eggs, 50 gms. of butter, 125 gms. of lean beef, 190 gms. of potatoes, 80 gms. of oatmeal, and contains 2-3 gms. of table salt.

sin). The fact of the matter is that even the absence of trypsin from the stool is not pathognomonic of pancreatic disturbance since Pratt(*b*) found it absent more than occasionally in normal individuals. Nor does the absence of digestion of the cell nuclei in the Schmidt or Kashiwado test necessarily indicate pancreatic disease, particularly when diarrhea is present (Brugsch).

In one case of achylia gastrica, with fatty stools, Junghans found trypsin absent in the duodenal contents; Von Kern and Wiener describe a similar clinical case but without any corroborative chemical data. Gross (*d*) pins his faith on the stool tests for trypsin, which he finds present in practically all disturbances and diseases, even intestinal disease. Therefore, in a case of total achylia gastrica with diarrhea, in which fecal trypsin was absent, he attributed the diarrhea to the diminished functional activity of the pancreas. Bittorf attributes the occasional diarrhea of achylia gastrica to thyroid overactivity as influencing intestinal motility. He denies the pancreatic etiology as a factor and says that achylia pancreatica is the rarest of phenomena.

It is important to note in the literature the array of data against the view of functional hyposecretion of the pancreas. Doblein, using stool tests for trypsin, Koziczkowsky, Einhorn(*b*), Okada, and Crohn found normal duodenal ferments in cases of complete achylia gastrica. H. Strauss found intestinal metabolism quite normal in cases of apepsia gastrica.

The general evidence, including metabolism studies, and the newer methods of duodenal content analysis, tend to throw much doubt on the existence of a functional pancreatic achylia. It is far safer as in the cases of Schmidt(*a*), of Junghans and of Spriggs and Leigh to attribute the metabolism disturbance (steatorrhea) to a pancreatic cirrhosis and atrophy. In fact Schmidt in his later paper, and Spriggs and Leigh, though entitling their contributions as pancreatic insufficiency, both concede a pancreatitis as the basis of the phenomena observed.

The Theory of an Internal Secretion of the Pancreas that Controls Food Absorption

Many data have been advanced favoring the theory of the control of pancreatic digestion by an internal secretion of that gland. Conceding the importance of the external secretion of the pancreas for the reduction of proteoses and peptones to amino-acids, and the saponification and splitting of fats, there is still much evidence that favors the view that absorption from the intestinal tract by means of the mucosal epithelium and the lacteals is under the control of an internal secretion or hormone. Favoring the hormone theory have been Lombroso(*a*), Fleckseder, Rosenberg, Oscar

Gross(*a*) and Brugsch. Those to whom the importance of the external secretion is paramount include Pflüger, Burkhardt, and Visentini; Pratt and his co-workers have never failed to emphasize the importance of the pancreatic juice reaching the intestine as the main factor in maintaining metabolism balance.

Allen says: "Neither of these hypotheses can be considered as fully established, and probably neither can be accepted in full form. The first gives suitable consideration to the external function of the pancreas, which, if not indispensable, is yet highly important. The second probably goes too far in attributing to the pancreas a special function governing absorption, but is correct in assuming that the pancreas has several functions, some of which may perhaps be performed by the acinar cells."

One specific internal secretion of the pancreas is conceded, namely, the hormone that regulates carbohydrate metabolism. Complete pancreatectomy invariably gives rise to severe diabetes, as the fundamental work of von Mering and Minkowski(*a*), and Sandmeyer has proven; the retention of as little as one tenth of the gland will prevent total diabetes. Furthermore, while not absolutely proven, the control of sugar metabolism is conceded to reside in the islands of Langerhans.

Yet there is no relationship between the clinical evidence of disturbance of the internal secretion that controls carbohydrate metabolism and that that controls intestinal metabolism. Only a small percentage of cases of well defined pancreatic disease have glycosuria (Fitz 11 out of 29 cases) and surely only the very rarest case of diabetes shows a disturbance of fat and nitrogen absorption indicative of pancreatic disease. If the carbohydrate regulatory function resides in the islet cells, then the absorptive hormone must be secreted elsewhere, and probably as a function of the true acinar cells of all, or of some part of gland.

That some other tissue or gland may function for the pancreas, or participate in its action is suggested by the work of McClure, Vincent and Pratt who found that in the absence of all pancreatic tissue, some absorption of fat and protein may still continue.

The Signs of Disease of the Pancreas

Clinically speaking, disease of the pancreas, however produced, is recognized in its fully developed chronic form by certain characteristic features. These signs include fatty diarrhea, that is numerous large, abundant oleaginous stools containing much partially digested proteid material, mainly meat fiber. "Fatty stools" as a symptom of pancreatic disease was described by Richard Bright in 1833. His own words best portray his meaning:—"The condition to which I refer is a peculiar condition of the alvine evacuation, a portion more or less con-

siderable assuming the character of an oily substance resembling fat, which either passes separately from the bowels or soon divides itself from the general mass and lies on the surface, sometimes forming a thick crust, particularly about the edges of the vessel (steatorrhea)." Similar observations have been made by Fles, Oser(*b*) and others.

To be strictly characteristic, the stools should be not only fatty, but large. The average weight of a normal stool (fresh state) of an individual on mixed diet, is 131 gms. (Pettenkofer and Voit(*a*)) of which 25.9 per cent or 34 gms. is solid substance. Schmidt(*a*) found normally the weight of fresh stool, collected over a 3-day period, on a prescribed "Schmidt diet," to be as follows:

	Fresh	Dried
Normal Individual	251.0 gms.	54.3 gms.
Obstruction of Bile Duct	944.0 "	175.6 "
Pancreatic Disturbance	2868.5 "	132.0 "

Pratt found in two cases of obstructive jaundice with malignant disease of the pancreas, that the weight of dried feces over a metabolism period of three days was 419 gms. in one case, and 355 gms. in another. In a patient with fatty diarrhea and glycosuria presumably of pancreatic origin but without icterus, the feces weighed 438 gms.

In a case of pancreatic insufficiency carefully studied Spriggs and Leigh report:—"The weight of the largest individual stool (fresh) was 1,944 gms.; the greatest amount of feces passed in 24 hours being 2,649 gms." or almost six pounds.

The stools are rarely watery; they do not resemble the stools of enteritis, or of fermentation diarrhea, or of gastrogenous diarrhea originating from achylia gastrica. Pancreatic stools are formed stools, fatty, heavy; liquid oil often runs off the side of the mass or collects on the surface of water. The color is a pale yellowish white or a mixture of clay color and streaks of yellow oil.

The color is not very different from that of a simple acholic stool, so much so that the attention of Walker was early called to the fact that the bile duct was freely open in one of his cases of pancreatic atrophy, yet the stools were colorless. He attributed this to some chemical reduction of the hydrobilirubin, though it is likely that the high fat content accounts for much of the pallor of the feces. The stools of tropical sprue or of tabes mesenterica may resemble pancreatic stools but the condition is easily clinically differentiated.

Microscopically, pancreatic stools are seen to contain much neutral fat floating as globules of highly refracting, oily material. Free fat in the feces is pathognomonic of pancreatic disease (providing of course that oil is not being administered either as a food or medication). Obstructive

jaundice may cause colorless large movements containing up to 45 per cent of fat (Brugsch), but never free neutral fat that is visible under the microscope or with the naked eye.

Nitrogenous metabolism disturbance is often indicated in pancreatic disease by the finding of large excesses of undigested muscle fibers, a phenomenon known as creatorrhea and described among others by Ehrmann. The phenomenon is dependent upon the inability of the digestive juices to digest muscle fibers and their nuclei, in the absence of pancreatic secretion. The striations of the meat fibers are clearly preserved and the particles, though small, are larger than those seen in normal stools and often have square or slightly rounded edges (Pratt(*b*)). Normally small particles of incompletely digested muscle fragments are seen; these may be more numerous in diarrheal conditions in which the intestinal motility is much hastened. But the finding of a large excess of such muscle particles is clearly indicative of pancreatic disturbance.

Increased amounts of fat in the diet, in the form of butter or lard are sometimes necessary to bring out typical fatty stools.

Clinical Occurrence of Steatorrhea and Creatorrhea

When Richard Bright first described fatty stools as characteristic of pancreatic disease, he immediately recognized the inconstancy of the symptom and the impossibility of harmonizing it with the pathological conditions of the gland. For the symptom was present in three cases of carcinomatous obstruction of both bile and pancreatic ducts, but was absent in three other similar cases, in two of which the pancreas itself was actually invaded by neoplasm. Fitz(*c*) in 1903 could find in the literature only 29 cases of fatty stools undoubtedly associated with pancreatic disease. Of these 29 cases, 12 had associated jaundice and 11 had diabetes. Von Mikulicz said that signs of functional disturbance in the stool do not appear until the greater portion of the gland is affected. This statement is corroborated by the fact that the author has observed a case of carcinomatous obstruction of the ducts, verified by duodenal analysis for ferments, in which no neutral fat or excess muscle fiber appeared for the first few weeks but did appear later in the disease. At the autopsy, the new growth was noted to have begun at the head of the gland, about the ducts, and to have subsequently invaded the body and part of the tail of the organ.

In the literature, all stools that have shown microscopically neutral fat, so-called "butter stools," have shown on chemical examination a large percentage of fat loss in the feces. The same observation holds for creatorrhea. Conversely, however, many cases with definitely disturbed nitrogen and fat absorption fail to show typical stools; in many of these, however, an in-

crease of diet can be made to bring out fatty stools, and undigested meat fibers.

Ad. Schmidt very recently makes the statement that fatty stools are more often and earlier a sign of chronic pancreatitis of gall-bladder origin. Tileston found typical "butter stools" in three out of six cases of pancreatic duct obstruction due to carcinoma; however, in all six cases, microscopic examination of the feces, when carefully and repeatedly performed, showed creatorrhea and steatorrhea to be present.

The Fractional Composition of the Fecal Fat in Pancreatic Disease

Normally fat appears in the feces in three forms, namely, neutral fat, fatty acids and soaps. The fat of the food is practically all in neutral form, the digestive splitting of neutral fats into its component fatty acids and soaps is regarded essentially as a function of the pancreatic juice, more particularly of its lipolytic ferment, steapsin.

In determinations on feces of normal individuals, Müller(*a*) found the proportions as follows:—neutral fat 24.3 per cent, fatty acids 35.3 per cent, soaps 40 per cent. That is, neutral fat composed about one quarter of the fecal fat.

In his early analysis of the feces of cases of pancreatic disease, Müller laid much stress on the disturbance in ratio between these three fractions. He asserted that there was a shifting of the index of fat splitting, so that more fat appeared in the neutral form. In pancreatic disease he observed the percentage of unsplit or neutral fat to rise to 50 to 77 per cent of the total fecal fat. He made an important diagnostic point of this observation.

Weintraud found 76.8 per cent and 72.5 per cent as neutral fat in two cases of pancreatic disease. Ehrmann found 57 per cent of the fecal fat as split fats, Fitz(*c*) in 9 of 11 cases in the literature found neutral fat distinctly greater than normal in pancreatic disease. These higher figures for unsplit fats are not confirmed by most of the other authors in the literature. Pratt(*b*) in 4 out of 7 cases found splitting slightly deficient, but not enough to be of diagnostic importance. Gross(*a*) found 65 to 87.5 per cent of fats split, Deucher 80 per cent, Keuthe 92.3 per cent, Albu 92 per cent, and Brugsch in only one case out of 15 found fat splitting under 70 per cent in pancreatic disease. Spriggs and Leigh found from 80 to 94 per cent of fat splitting in a well studied case of atrophy of the pancreas.

Experimentally, Brugsch found normal splittting at different levels of the intestinal tract of dogs in which the ducts had been tied and the pancreas caused to atrophy.

Under these circumstances, it is natural to conclude that the fainter

lipolytic ferments of the stomach, bile and succus entericus replace the loss of the pancreatic steapsin. Stade showed that under certain conditions, gastric juice alone could split fats up to 50 to 60 per cent. The theory that the intestinal bacteria accomplish splitting in the absence of pancreatic juice is refuted by the experiments of Müller(*a*); he was unable to obtain more than 9 to 13 per cent of split fats in prolonged experiments *in vitro*.

Zoja called attention to the low percentage of soaps in the stool of pancreatic disease, a fact which has been attributed to the diminished calcium content of the fat in the disease of secreting pancreas. Hedon and Ville found that after experimental removal of the pancreas in dogs, that soaps disappeared from the stool. Visentini found on tying the pancreatic duct that much fat was lost, most of it as neutral fat and fatty acids. On the other hand, Pratt, Lamson and Marks, Rosenberg and Hedon and Ville found good splitting on tying off the ducts.

The quantity of soaps in the normal stool varies widely. The chemical methods for analysis of soaps are open to criticism, and it is impossible to deduce from the innumerable analyses in the literature any diagnostic significance in the soap content of the feces.

Abelmann made the point that in partial extirpation of the pancreas total fat absorption on a moderate fat ration was about 50 per cent; when the dietary fat intake was liberally increased the fat absorption fell to 31.5 per cent. When fat in emulsified form was given (milk) absorption rose to 80 per cent. Sandmeyer, on the other hand, found only 42 per cent of milk fat absorbed, while meat fats varied in absorption between 0 and 78 per cent. Hedon and Ville found that after tying the biliary ducts and performing incomplete pancreatectomy in dogs that only 10 per cent of non-emulsified fat was absorbed, while 22 per cent of milk fat was taken up.

Some interesting observations have been made by Spriggs and Leigh in a well defined case of chronic pancreatitis. They showed that if the fat intake is doubled, the absorption falls to about half, though the splitting is the same; that the absorption of fat when administered as new milk reaches a much higher figure than when given as cream or butter (non-emulsified form). Hence it is not the character of the fat but its form (emulsification) that benefits its absorption.

Butter fat was no better absorbed than meat fat, a fact which created surprise, since the fats of low melting point are supposed to be better absorbed than those with higher melting point (Schmidt(*c*)). Cod liver oil caused an exacerbation of the subjective distress and diarrhea; little of the oil was absorbed.

A marked increase of lecithin excretion was noted by Erhmann in the feces of a case of chronic pancreatitis (3.6 per cent against a normal lecithin excretion of 0.51 per cent).

Pancreatic Infantilism.—Byron Bramwell in 1904 described as a new clinical entity a case of arrested development, which he attributed to pancreatic deficiency. He described a boy of 18 years and 6 months, whose physical development was normal up to 11 years of age and then ceased. He was a bright, intelligent boy, perfectly formed, except for abdominal enlargement. His height was four feet four and one eighth inches, his weight seventy-one and a half pounds. He had had diarrhea for nine years. Under observation his stools were frequent, and fatty and large. The Sahli test for trypsin in the intestine was negative. Under treatment with pancreatic extract for two years, the diarrhea ceased, the stool became more normal in appearance, the boy grew 5⅜ inches in height, and added 22 lbs. to his weight. Pubic hair appeared and his sexual development became more normal.

Rentoul in the same year described a similar case in a girl 18 years of age, whose growth was arrested at the age of eleven years. She had had diarrhea from infancy, with abdominal enlargement. Her stools were described as "of foamy oily nature, very large and floated." In five months' treatment she gained nine and a half pounds and grew two inches, with the development of sexual characteristics.

Langdon Brown(*b*) described a like case in a boy of sixteen years who was suffering from a severe form of congenital syphilis. The boy appeared to be eight or ten years old. At autopsy a syphilitic pancreatitis with pancreatic atrophy was seen; there had been no glycosuria.

Two cases were reported by Thomas. The first a man of twenty-four years with the size and stature of a boy of ten; the second a youth of 18 years, who had the appearance of a boy of 8 or 9 years. Both patients suffered from a lasting intractable diarrhea.

Recently Bullrich described a typical case of pancreatic infantilism with necropsy findings. The boy had been normal and well grown up to his eleventh year when he began to lose weight; he developed glycosuria at sixteen years. At the age of twenty years he was four feet tall, and weighed forty-seven pounds. For eight months he had a severe diarrhea. The urine contained from 3.8 to 4.5 per cent of sugar. At autopsy, a pericanalicular cirrhosis of the pancreas and liver were found. The thyroid was undeveloped. Bullrich ascribes the disease to a pluriglandular disturbance in which the pancreatic deficiency preponderated.

In a similar class may be put the unique case described by Garrod and Hurtley(*c*) in a boy of six years who from birth had shown a clear cut and typical steatorrhea. The boy was otherwise in good health and spirits and his development was normal for his age. The stools were liquid, fatty and rapidly became rancid in summer. Chemical tests failed to show a deficiency of trypsin. The disturbance of fat metabolism was evident; only 69 to 74 per cent of the fat in the diet was absorbed. In the feces splitting was fair, 34.2 to 68 per cent; soaps were very low, 0.6 per cent

to 22.5 per cent. No improvement was seen under specific pancreatic therapy.

It is of interest that a brother of this child who died in infancy also showed steatorrhea.

Robson and Cammidge express as their opinion the fact that these cases are instances in which the pancreas is sufficient up to about the age of eleven; about the time of puberty physical and sexual development is arrested. The actual pancreatic disease is however probably congenital since in most of these cases the alvine defecations were present from birth. The only exact chemical data in congenital pancreatic disease are those of Garrod and Hurtley(*c*); their figures indicate definite metabolic disturbance of the pancreatic function.

Opotherapy in Pancreatic Disease.—This is an interesting and developing chapter in the field of metabolism disturbances.

Abelmann found in partial pancreatectomized animals, that a protein absorption of only 30 to 80 per cent could be raised and maintained at 74 to 78 per cent by the feeding of raw pancreas gland. After total pancreatectomy a total loss of fat is converted into a considerable absorption of fat on gland therapy. Sandmeyer found similar results. Pratt, Lamson and Marks found in dogs with the pancreatic ducts tied off, that considerable improvement in absorption resulted from feeding raw gland to the animals; pancreatic extracts were less efficacious, the pankreon in one experiment brought the fat absorption up from 11.3 per cent to 48.5 per cent and the nitrogen absorption from 22.2 to 52.1 per cent. Lombroso(*b*) on the other hand failed to find improvement in the absorptive capacity of his dogs after exhibiting to them pancreatic broths, or pancreatic extract or even the duodenal juice of a healthy animal.

In general, pancreatic extracts, or the fresh gland when administered, have shown beneficial results at the bedside. Weintraud with pancreatin, Harley with the whole gland, Salomon with pankreon (a commercial dry extract hardened with tannin), Ernst Meyer with a combination of pankreon and opium all found marked improvement. The last showed by exact chemical data that absorption of nitrogen and fat was almost doubled. Oscar Gross(*a*) found pankreon useless but asserts that the fresh pig's gland greatly improves absorption.

Masuyama and Schild found marked improvement with pankreon. Thus on a mixed diet there was a utilization of 36.9 per cent fat and 37.2 per cent protein; after exhibiting the raw gland absorption rose to 63.6 and 45.3 per cent respectively.

Glaessner and Sigel demonstrated chemically the best results with pancreatin and bicarbonate of soda. Empirically, Barbour(*a*) tried to improve absorption by hydrochloric acid administration, hoping to stimulate secretion and thus the flow of pancreatic juice. No result was seen, but a good result is reported with pancreatin and calcium carbonate.

Mosenthal, in a case of chronic pancreatitis (probably due to a pancreatic calculus) and associated with severe diabetes, studied the effects of gland therapy. Pankreon gave no results, but raw sheep's pancreas prepared as a salad in 50 gm. portions, three times a day, brought a very marked improvement. "The stools changed from those typical of pancreatic disease to what appeared to be normal movements." (Mosenthal (*a*).) A dangerous acidosis however intervened to cut short the experiment; Salomon had previously demonstrated increased amounts of acetone in the urine under pancreatic therapy.

Tileston found some improvement after HCl therapy; decided benefit mathematically demonstrable was seen after pankreon or raw pancreas feeding (0.2 gm. three times daily). Spriggs and Leigh employed in successive periods practically all the commercial and raw gland forms of pancreas, with little result. They thought that such preparations, with the exception of trypsogen tablets, irritate the intestinal tract and brought no improvement.

Any doubt however about the benefits of the clinical administration of pancreatic extracts or of the raw gland is answered apparently by the striking improvement shown in the cases of pancreatic infantilism (Bramwell, Rentoul and others).

In general, opotherapy of the pancreas seems very encouraging, and at least in some of the cases to approach a specific effect.

The improvement resulting from the oral administration of gland extracts has been held as a proof of the fact that the external secretion of the gland controls digestion and absorption. There is however this fact to consider, that with even excessive feeding of commercial extracts, no ferments were demonstrable in the feces, though the absorption of food had improved. The improvement in absorption after feeding the gland is beyond question. The explanation lies in the fact that both commercial and raw extracts probably contain the hormone of the gland in an active form, just as does thyroid gland or its derivatives for its specific hormone.

Prognosis of Pancreatic Disease.—The prognosis and duration of pancreatic disease depend in great part upon the etiology and clinical course. In the absence of malignant neoplasms, the characteristic fat and protein absorption derangement in itself does not necessarily shorten life materially. Cases of steatorrhea and creatorrhea of even apparently severe form have been under observation for 26 years (Walker). Spontaneous cure or improvement in the intestinal symptoms is clearly possible as witness the remarkable improvement in the absorptive power of the patient of Glaessner and Sigel when observed a few years later by Keuthe. The disturbance of metabolism that occasionally forms part of the picture of acute pancreatitis may, with clinical postoperative treatment, almost disappear, as occurred in the case of abscess of the pancreas reported by Brugsch and Koenig.

The specific gland therapy, as remarkable as it appears, seems limited by the fact that the improvement can be maintained only while the gland or its extract is being administered.

The Phenomenon of Acute Toxic Necrosis of the Pancreas—"Fat Necrosis."

The pancreas suffers occasionally from a disease characterized by an acute inflammatory, often hemorrhagic degeneration and necrosis, a form of toxic disintegration which is quite peculiar unto itself. As we regard it to-day, it is essentially a nonbacterial disease, one in which an activation of the proenzymes of the gland leads to its own destruction with the origination of an acute severe intoxication that leads to death in the majority of cases.

One of the quite characteristic features of the disease is the appearance in the parapancreatic and peripancreatic and subperitoneal tissues of areas of fat necrosis. In the course of the last few years our conception of the mechanism of the production of this severe degeneration has undergone much change as the result of encompassing and thorough experimental and chemical research; a review of this literature is essential to the understanding of our present day conception.

Balser in 1882 first described the small opaque white areas in the parapancreatic tissues and interacinous tissues of the gland. He discovered these spots in careful routine examination of post mortem material; his microscopic examination showed them to consist of necrotic fat cells. They were found in five out of twenty-five bodies examined. Occasionally these focal areas were found in more distant areas, thus forming disseminated fat necrosis. Chiari, who confirmed the observation of Balser, drew attention to the fact that their occurrence was associated in five cases with severe disease of the pancreas.

The essential nature of the process was first explained by Langerhans who demonstrated that the areas were composed of necrotic fat tissue, consisting of fatty acid crystals and glycerin; in long standing cases calcium soaps had been laid down. The soluble glycerin had been absorbed and the fatty acid crystals filled the necrotic fat cell.

Many chemical confirmations followed in the succeeding years; the necrotic areas were observed over a more extensive region, namely in the subperitoneal and subcutaneous tissues, in the subpericardial and even by Von Hansemann in two cases in the subendocardial tissues.

The earliest interpretation put upon their presence by Balser, Langerhans, Ponfick, Dieckhoff and others regarded the areas as essential fat necrosis; the disease of the pancreas, when present, they regarded as secondary and sequential. Fitz(*a*) and later Korte laid the foundation of our

modern day conception by attributing primarily to the inflammatory disease of the pancreas this peculiar phenomenon.

In the current enthusiasm of the day for bacteriology it was not surprising that the process should have been attributed to bacterial agents. Many bacteria were found; in some as many as four varieties of bacteria were described. The most common organism, the B. coli communis, was identified by Welch in a case of acute pancreatitis with fat necrosis.

Subsequent observations by Frankel, and again by Sawyer who cultured directly the necrotic areas, failed to confirm the bacterial origin of the lesion, either directly by cultures or by microscopic examinations of the hardened tissues. The eventual conception of Hlava, Fitz and Welch was that the bacteria were present as secondary invaders rather than as etiologic factors in the production of the disease.

The admirable clinical description by Fitz(*a*) of the forms of acute pancreatitis, and of its association with fat necrosis, concentrated attention on the pancreas as the important etiological agent. During the next decade numerous attempts were made to reproduce experimentally the pathological picture of the disease. Langerhans injected into the fat tissue of rabbits an infusion of the pancreas and succeeded in one case in producing a small area of fat necrosis in the perirenal tissues of the animal. Jung utilized pieces of fresh pancreas, aseptically obtained, and inserted the tissue into the peritoneal cavity; in one experiment he noted numerous areas of fat necrosis. Hildebrand and also Dettmer made a more direct attack upon the pancreas; they produced fat necrosis by simply tying off the pancreatic ducts, assisting this procedure by incising the gland and allowing the pancreatic juice to flow directly into the peritoneal cavity (Milisch). Injections of trypsin alone did not produce the lesion, hence the active factor was to be regarded as partly the lipolytic ferment steapsin. These experiments were repeated in more or less similar form by Flexner(*a*), Oser(*a*), Korte and others with like results. Blume found that simple obstruction of the circulation of a portion of the gland for a few minutes caused hemorrhagic infiltration and fat necrosis. Flexner(*a*) demonstrated the actual presence of a lipolytic ferment in the areas of fat necrosis.

The difficulty in the explanation of the phenomenon lay, however, in the fact that no explanation could be given for the focal necrosis in distant areas not directly exposed to the escaping pancreatic secretion. Gulecke created an intraperitoneal fistula of the Wirsungian duct and demonstrated fat necrosis in the immediate area. Milisch similarly concluded that the escape of pancreatic secretion into the peritoneal cavity was the deciding actor, both experimentally and clinically.

Opie(*a*), in a large series of experiments, tied the ducts in cats and produced in six instances experimental fat necrosis not only in the surrounding tissues but also in the subcutaneous and subpericardial fat. Those

animals that survived the longest, twenty to twenty-five days, showed the most extensive areas of necrosis even as far as the symphysis pubis, retroperitoneal fat and pericardium. There was apparently no escape of pancreatic fluid to account for the phenomenon in Opie's work; the pancreas was firm and small. Direct implantation of the end of the Wirsungian duct into the subcutaneous tissues of the abdominal wall caused extensive fat necrosis in the abdominal thoracic walls, but not within the mesentery or omentum where in previous experiments it had been more commonly found. The gland itself had remained practically undisturbed.

Gulecke produced pancreatic necrosis by injection into the ducts of various irritants and observed fat necrosis in practically all his experiments. In six animals he carefully walled off the pancreas; the necrosis was thus limited in area; no fat necrosis was seen in the general peritoneal cavity. He attributed the wide distribution of fat necrosis clinically, to direct diffusion or lymph-vessel transportation. This view was later upheld by Eppinger(*a*), and was the conclusion to which Opie(*a*) independently had arrived. Gulecke's conclusions were that primarily necrosis of the gland takes place with the diffusion of the lipolytic ferment by lymphatic paths through the tissues.

Paralleling this line of experimentation is a series of attempts directly to cause pancreatic necrosis and inflammation, and in this way indirectly to reproduce fat necrosis. Hemorrhagic pancreatitis had been produced by Thiroloix by injection of zinc chlorid within the pancreatic duct of a dog; Hlava injected artificial gastric juice and caused hemorrhagic infiltration of the pancreas and fat necrosis. In a similar manner, inflammatory infiltration of the pancreas has been caused by the injection within the duct of bacterial cultures, diphtheria toxin, olive oil (Oser(*a*), Hess (*a*)), intestinal secretion or commercial trypsin (Polya), bile (Gulecke, Flexner(*a*), Opie(*a*) and others).

Flexner, in his earlier work, used dilute hydrochloric acid in strengths varying from ½ to 2 per cent and succeeded repeatedly in creating the picture of acute pancreatic inflammation with typical fat necrosis. Similar success attended the attempts with sodium hydrochlorid, bacterial cultures and suspensions, formaldehyd, etc.

At first it was suggested (Hlava) that the infecting or activating agent was intestinal secretion forced by duodenal retroperistalsis into the pancreatic passages. Experimentally, this could not be reproduced; more recently Seidel again caused artificial duodenal stasis without reproducing pancreatic disease by regurgitation.

The association of gall stones and diseases of the bile passages with pancreatitis was suggested clinically by Lancereaux, Oser(*a*), and also Korte but the first clear definition of the theory as well as illustration of its mechanism was advanced by Opie(*c*) in 1901.

Opie reported a case of acute pancreatitis at which at autopsy a small gall stone was found impacted in the common bile duct near the papilla. The lesser peritoneal cavity was the site of an abscess surrounded by fat necrotic tissue. The face of the pancreas was covered by hemorrhage. Opie collected many similar cases from the literature in which gangrenous or hemorrhagic pancreatitis was associated with gall stones lodged at or near the common orifice of the ducts.

A second case furnished Opie(*c*) with the mechanism by which a pancreatitis was produced. In this case, the diverticulum of Vater was unusual in length, 10 mm.; the orifice into the duodenum measured 5 mm. In the diverticulum was found a calculus 3 mm. in diameter. Such a calculus by plugging the Vaterian orifice would convert the common bile duct and pancreatic ducts into a continuous open channel and thus divert the bile into the Wirsungian or associated ducts. This is the mechanism advanced by Opie as explaining the phenomenon.

Not alone the impaction of a gall stone in the common duct is essential for in many cases, apart from trauma, no gall stones are found. In recent years study has been directed toward the sphincter of Oddi, the sphincter that guards the papilla of Vater at its point of junction with the duodenum. Meltzer attributed to spasm of this sphincter some forms of obstructive jaundice and its importance in regulating the expulsion of bile and pancreatic juice has come more and more into the foreground. The experiments of Williams and Busch show that by passing glass balls through the sphincter, dilatation of the sphincter was caused with resultant pancreatic necrosis, due to regurgitation of intestinal contents. It had been previously shown that duodenal stasis alone would not cause regurgitation into the ducts when the sphincter was intact (Seidel). The added injury to the sphincter caused by the glass balls, analogous to gall stones, might well be one of the deciding factors.

Archibald showed that experimentally a pressure of even 1000 mm. of water in the gall bladder was unable to force an iron solution into the pancreatic ducts, when the sphincter was ligated. However, a pressure within the bile ducts of from 300 to 800 mm. of water was sufficient to flood the pancreatic ducts. If the bile salts alone or sterile bile was used a moderate reaction comparable to a subacute pancreatitis resulted; if to the bile there was added a bacterial culture, a severe acute pancreatitis necrosis and death resulted, in one cat within twenty minutes. Archibald attributed the necrosis of the pancreas to the chemical action of the irritant employed. Infected bile acted not by bacterial activity but by the chemical changes produced in the bile by the innoculated bacteria.

Opie(*b*) experimentally reproduced pancreatic necrosis in animals by injecting sterile bile into the pancreatic ducts, subsequently ligaturing the orifice of the duct. Hemorrhagic pancreatitis and fat necrosis resulted.

The incidence of hemorrhage with the inflammatory reaction in the pancreas was attributed to injury and necrosis of the adjacent blood vessels, even before the inflammatory reaction in the gland tissue itself was well marked. Where a large vessel is involved, the hemorrhagic aspect of the clinical case predominates, thus giving the case the appearance of pancreatic hemorrhage, so called "pancreatic apoplexy." These cases are now all regarded as mere phases of pancreatic inflammation and necrosis (Pratt(*b*)). To the activation of the proenzyme trypsinogen and the potency of steapsin increased by the entrance of bile (as well as by other substances) was attributed, the necrosis and self-digestion of the pancreas; the liberation of its activated ferment (steapsin) caused the fat necrosis. A further injurious influence was attributed to the saponification of fats due to the simultaneous activation of the pancreatic lipase with damage to the pancreatic tissue by the fatty acids and more particularly the soaps so formed (Hess(*a*)).

These important experiments were a few years later confirmed and added to by Polya. By the injection into the pancreatic ducts of activated trypsin, or commercial trypsin, as well as of enterokinase and succus entericus, experimental pancreatitis was successfully reproduced. If the trypsin were heated the effect was lost. Activated pancreatic secretion acted in the same way as activated trypsin and similarly lost this power when heated. The injection of activated substances during the digesting state of the gland, while not essential, gave the most striking results (Hess(*a*)). That autodigestion of the pancreas spontaneously took place post mortem had been amply pointed out by Chiari(*b*).

The Toxic Element in Pancreatic Necrosis.—The above mentioned experiments and observations did much toward clarifying our conceptions of the mechanism of production, and the chemical nature of pancreatic necrosis. The actual toxic agent producing the fulminating symptoms and death in pancreatitis remained however in doubt. The experiments of Hess, Gulecke, Polya and others had demonstrated that the insertion of pieces of pancreatic tissue, or the creation of an intraperitoneal pancreatic fistula led to a severe toxic reaction and often to death. The toxic reaction was generally attributed to the *absorption of pancreatic secretion* containing activated ferments. Both the trypsin and steapsin were independently held responsible for the fatal outcome of the experiments. Many authors had shown that the intravenous injection of pancreatic juice activated with intestinal secretion produced toxic death.

Von Bergmann and Gulecke doubted that trypsin was the sole toxic agent and attributed to another chemical toxin derived from the necrotic pancreas the severe phenomena induced. They showed that autolyzed pancreatic tissue was much more toxic than fresh tissue, and that pancreatic broth was still more poisonous in its effects when injected intraperitoneally.

In a series of experiments these authors were able to demonstrate, by previous injections of trypsin, a degree of acquired immunity in the animals. Experimental pancreatitis produced in these animals by injection of oil into the Wirsungian duct caused pancreatic necrosis and atrophy, but not death nor toxic collapse. Von Bergmann and Gulecke specifically state that they do not understand death in pancreatic disease as due either to the trypsin or steapsin liberated; they attributed the fatal outcome to a toxic protein formed in the autolyzing pancreatic tissue; in their experiments they utilized trypsin as an agent with which to immunize against this unknown toxin.

The researches of Lattes have added much to our conception of the formation of this toxic product. The intraperitoneal injection of pancreatic juice in which the trypsin was inactivated, though the steapsin was active, failed to produce an effect in dogs. The injection however of activated fluid from a pancreatic fistula caused toxic death in a few hours with symptoms of collapse, peritonitis, hemorrhage and acute nephritis. The same phenomena were seen in all experiments, independent of whether the lipolytic ferment of the injected fluid was active or not.

Intraperitoneal fistula caused fat necrosis but no dangerous symptoms in the animal, unless duodenal juice was injected as an activating substance. In the latter case death took place within nine hours. Lattes concludes that the fatal intoxication is due to increased potency of the proteolytic power of the pancreas when activated by intestinal juice. The toxin thus produced, while thermolabile, is more stable than the proteolytic ferment, and can in this way be separated from it. Pure autolyzed pancreatic tissue, injected, was ineffectual, as was also the inactivated pancreatic juice. Both injected at once caused rapid death with fat necrosis.

Death in trauma or rupture of the pancreas is due to activation of the liberated pancreatic secretion by the necrosing tissue cells. Ligation of the vessels of the gland after experimental traumatism to the gland results in acute pancreatic necrosis often with death in animals (Lattes). Levin places emphasis on the interference with circulation as being an essential factor. Lacking this, even severe crushing or ligaturing does not necessarily produce acute necrosis or a fatal result.

Since 1916, the American literature has contained several important contributions tending more accurately to identify the toxic protein element in pancreatic necrosis. In that year Whipple announced the isolation from the pancreas of an animal in which an experimental hemorrhagic necrosis had been produced, of a toxic proteose which he considered an active agent in the production of the symptoms. This proteose he regarded as analogous to the proteose he had demonstrated in acute intestinal obstruction and in acute peritonitis. Petersen, Jobling and Eggstein have shown that in experimental acute pancreatitis the incoagulable nitrogen of the

blood was increased. They assumed "that death was due to flooding of the blood stream with higher split products formed at the expense of the pancreatic tissue, of which the proteose increase is an index." They found a definite increase in the antiferment content of the blood and regarded this as a protective phenomenon favoring recovery. The injection of trypsin into the duct gave the picture of a true tryptic shock with fatal result; serum protein was markedly increased, while the protective tryptic antiferment had markedly diminished. Injection of soaps into the duct gave a less severe and quite different reaction.

Goodpasture(*b*), by chemical means, separated from the fresh normal pancreas of a dog a thermostabile toxic element, present in the β-nucleoprotein fraction, probably protein in nature. Minute doses of the purified substance produced in dogs symptoms comparable to spontaneous hemorrhagic necrosis of the pancreas.

Is the peritoneal exudate that occurs in toxic pancreatic necrosis itself toxic and what are the virtues of operative interference for draining this exudate? To this hypothesis Whipple and Goodpasture devoted themselves. They demonstrated the presence of protective antiferments in the serum and blood plasma in experimental pancreatitis.

The peritoneal exudate of a dog suffering from experimental pancreatic necrosis was injected intraperitoneally into a healthy animal. The dog remained well. Nor was a toxic effect seen when the peritoneal exudate was injected intravenously.

In a dog suffering from the effects of a severe hemorrhagic pancreatitis the peritoneal exudate of a similarly affected dog was injected intravenously and again intraperitoneally without increasing the gravity of the symptoms. In fact the dogs from whom the exudate was taken remained more sick than those into whom it was injected, the latter recovering completely.

They conclude that the peritoneal exudate is one of the protective phenomena of pancreatic necrosis, and that its operative removal and drainage is not only dangerous but needless.

From the mass of the above detail experimental and clinical data one may deduce the modus operandi of hemorrhagic pancreatitis and necrosis in the following manner. Intrapancreatic activation of protrypsin and steapsin takes place due to the entrance of infected bile or intestinal secretion or perhaps spontaneously; or again in traumatic cases by bruising or rupture of the intestine. The activated ferments cause necrosis and autolysis of the parenchyma with the absorption of an unknown toxic agent, in all likelihood proteose in nature. The degree of damage to the secreting cells determines the degree of necrosis, gangrene, or hemorrhagic destruction (damage to the blood vessels) that will ensue. The body reacts to the absorption of the toxic protein by increase of anti-ferment in the blood, by the appearance of protective specific substances in the blood

(Sailer and Speese) and by the production of a protective peritoneal exudate. Fat necrosis as a phenomenon of toxic pancreatic necrosis is due to transmigration of activated steapsin by lymphatic passages with resultant splitting in areas of the neutral fat in the subperitoneal tissues.

The Relation of Dermatoses to Metabolic Disturbances

. . . . . *Walter James Highman and Jeffrey C. Michael*

Dermatoses Conceived to be Due to or Associated with Digestive Disturbances —Dermatoses Conceived to be Due to or Associated with Diet—Dermatoses Conceived to be Due to or Associated with Cardiovascular Disease—Dermatoses Conceived to be Due to or Associated with Renal Disease—Dermatoses Conceived to be Due to or Associated with Nervous Diseases —Dermatoses Conceived to be Due to or Associated with Respiratory Diseases—Dermatoses Conceived to be Due to or Associated with Endocrine Disturbances—Dermatoses Conceived to be Due to or Associated with Disturbed Nitrogen Metabolism—Dermatoses Conceived to be Due to or Associated with Carbohydrate Metabolism—Dermatoses Conceived to be Due to or Associated with Miscellaneous Causes—Acne or Acne Vulgaris —Acroasphyxia—Dermatitis—Dermatitis Exfoliativa—Dermatitis Herpetiformis—Erythema Multiforme—Furunculosis—Gangrenes—Pemphigus—Prurigo—Psoriasis—Rosacea—Seborrhea—Urticaria—Xanthoma.

The Relation of Dermatoses to Metabolic Disturbances

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Tentative as must still remain our views on the relation of dermatoses to general disturbances, we cannot evade the fact that in many skin diseases such a relationship exists. Positive knowledge thereof is slight. Our ignorance depends largely upon the fact that chemical and other laboratory methods of gathering evidence are in themselves still inadequate. The etiology of many dermatoses will continue to remain obscure until internists and biochemists can bring the light. This does not exonerate the dermatologist, for in the proper sense he is an internist who knows the skin, and his responsibility does not end with the subcutaneous tissue.

Clinical study, alone, has distinct limitations. Without underrating its value in the least, a method so largely subjective, so impalpable, can scarcely be expected to supply foundations. Any one reading descriptions of the same episode written by their several reporters for various newspapers will understand the restrictions inherent in the purely clinical method of stating medical beliefs. We need facts and figures to determine the relationship between skin and general diseases, and despite the shrewdest surmises of which we may be capable, with reference to the existence of this interrelationship, precisely what we lack are facts and figures.

There are also objective difficulties; diseases that look alike may have entirely dissimilar causes, as the zosterform eruption of arsenic, and the ordinary zoster; or the urticaria due to a certain proteid, and the urticaria of syphilis. The mere matter of appearance does not determine a clinical entity. It is the appearance of abnormal tissue together with a knowledge of the mechanism producing it that are required to establish a disease as a thing apart. The morbiliform eruption of belladonna, arsphenamin, and measles itself, is the same so far as the skin is concerned, and yet how different is each condition when one reflects on the cause. Thus ob-

jectively, too, there are great limitations to our ability to widen the scope of actual knowledge.

Tradition brings further burdens of complexity—the nomenclature in dermatology. It is overwhelming to read the number of terms applied to the same clinical condition. We cannot go too far in eliminating accepted designations, for clinically identical conditions may pathogenetically not be the same; nor can we venture too far in clinical differentiation, for dissimilar looking dermatoses may have the same causation. Still, overelaboration of language is always a handicap. Thus dermatology remains a speculative science in which the objective data are not entirely reliable, the designations often inapt, if not actually incorrect, and to which methods of investigation, in themselves inadequate, have not yet been applied even indifferently well.

Nevertheless, it is obvious that, although the skin is subject to many local disturbances, there must be many which participate in, or cause, or reflect general disturbances. The skin, no more than any other organ or tissue, can follow an entirely autonomous pathological career. Many of its disturbances must depend upon factors in the general body economy. It is difficult to trace these. In the very sparse literature all views are in conflict. One author reports a series of conditions associated with hyperglycemia; other investigators find another group. A diminished alkali reserve is found in certain dermatoses by one, and in others, by another, and so it goes. Nor is there any reason to assume that a relationship such as that indicated in the previous sentence is more than coincidence, unless practical application of the findings supports another view. In furunculosis, for example, hyperglycemia is often present, and in diabetes furunculosis often arises. Reducing the starch intake often limits or cures the cutaneous manifestation. Here there is something suggestive of cause and effect. This is exceptional.

Yet the toxic erythemas, arising as they do in sepsis, in follicular tonsilitis, and in intolerance to drugs such as atropin, arsenic, copaiba, phenolphthalein, etc., indicate that our ignorance of the causation of dermatoses depends entirely upon our inability to discover facts. The relation of the multiform erythemas to rheumatism or to asthma substantiates this view. The association of primary purpuras with visceral disturbances in scurvy and perhaps pellagra, and the relation of these to imbalanced diet; and of urticaria to specific food poisoning—all give some idea, however impressionistic, of the dependence of skin manifestations upon remote causes. The leucemias provoke dermatoses, the pathogenic mechanism of which is in part metabolic derangement, and in part not. The first are erythemas, toxic in character, and anatomically not suggestive of leucemia. The second are actual leucemic infiltrations resembling various dermatoses that are in no wise leucemic. Even Hodgkin's disease may involve the skin, producing characteristic tumors containing Dorothy Reed cells, as

Howard Fox has shown. There is almost no group of general disturbances that does not, in one way or another, involve the skin.

The integument may be the starting point of disease, as in mycosis fungoides, but more commonly it is merely a participant. All of the examples cited in the previous paragraph attest to this. Before embarking upon further details, however, it will be necessary to elaborate certain facts, already hinted at, realization of which is fundamental to a broader understanding of dermatoses. A generation ago Besnier postulated the doctrine of skin reactions, a trite enough concept, perhaps, and yet comprehension is intimately involved in reiteration of the obvious. It must be grasped that abnormal tissue responses present a restricted range of possibilities. Thus a certain clinical picture, definite enough objectively, may have many causes; thus urticaria may be due to scores of foods, to syphilis, to the nettle, or to the jellyfish (actinozoa). The mechanism may be prevailingly anaphylactic, but the agents are legion. Conversely, a single agent may evoke several pictures, subject to biochemical factors we cannot yet envisage. The bromids serve as an example. They may provoke erythemas, vesicles, pustules, or granulomas. If so many factors may produce a single objective phenomenon like urticaria; or one factor, as the bromids, may produce so varied a series of phenomena, it is easy to grasp that concepts in clinical dermatology are subject to enormous excursions into the field of error, largely subjective, but what is worse, more largely indeed objective.

With the difficulties, then, of the theme in mind, let us try to define the subject of this thesis. Eliminating anomalies, infections, and neoplasms, those dermatoses will be dealt with which are prevailingly inflammatory, and the etiology of which is obscure. What is known of their causation depends upon circumstantial evidence which supports the belief that they are related to or depend upon general disturbances. It is the object of this exposition to mention what little is known, and whatever additional may be surmised.

Dermatoses Conceived to be Due to or Associated with Digestive Disturbances

Dermatoses have been associated with digestive disturbances as indeterminate as mere constipation, or as concrete as fat or starch indigestion. Johnston ascribed the seborrheas, and particularly acne, to starch indigestion. Towle and Talbot considered infantile eczema due to either fat or carbohydrate indigestion; in a grosser form solid, undigested food particles were demonstrable in the stools. The former was more exudative in character; the latter more chronic. Czerny, years ago, ascribed infantile eczema to the "exudative diathesis," a condition oc-

curring in overfed infants. Fatty stools, or stools with undigested food, were, he believed, associated with this condition.

The adult form of eczema has been widely ascribed to proteid indigestion. It is difficult to define the relationship. Without questioning the advisability of treating any digestive disturbance, it may be questioned whether any one has ever seen a dermatosis of the above class disappear under treatment of the alimentary canal alone, without suitable local management. Only such a control would provide positive evidence. Nevertheless, clinical experience is replete with evidence that certain dermatoses depend for their very existence upon digestive diseases. Rosacea is of this number. Aside from those cases ascribed to alcoholism and tea drinking, the great majority are conceded to be caused by chronic gastritis, gastric ulcer, hyperacidity (whatever that may mean) and remoter conditions underlying or associated with these, as well as by functional gastric derangements, if there really are any, including vagotonia. The conventional use of these terms will be pardoned, for so employed they convey something, in spite of their indefiniteness. Undoubtedly rosacea may be controlled by controlling the gastric condition.

In a less direct manner acne vulgaris has a similar relation to these conditions. Acne vulgaris is a disease with marked features. It arises in relation to puberty and disappears with the establishment of sexual stability after adolescence. Many of its victims present hyperglycemia, and have slightly enlarged thyroid glands. Whether this picture hangs together as a unit or not cannot be stated, for doubtless many people have acne who have no other ascertainable derangement. Although in the majority of cases acne will disappear under *x*-ray treatment, in some it will not without the cure of the underlying gastric or gastro-intestinal disturbance, even if this be only constipation.

It is impossible to discuss this phase of the subject without further reference to eczema. This disease, if it be a disease, a matter subject to reasonable doubt, has been divided, etiologically, into two groups, one acknowledged to be the result of some external irritant, the other of an internal derangement. In the second group the alimentary tract has been most widely incriminated. As time has advanced evidence has been accumulated that has forced, more and more, the reallocation of eczema types, placing the majority of cases in the group due to external causes. The day will arrive when the entire literature on eczema will be read, if at all, only for the historic amusement it may furnish. There is absolutely no convincing proof that this dermatosis has any relation to the alimentary tract, unless it is to be found in writings on pediatrics; the opinion is here ventured that more babies have been starved than cured by trying to treat their skin through their intestines. Physicians have been forced by anxious mothers to sacrifice offspring at the altar of maternal neuroses.

Pruritus ani has been widely ascribed to acid stools. There is something to be said in favor of this belief, although the literature reflects nothing thereof. Beyond question many cases of anal itching are relieved only after a demonstrated intestinal disorder has been controlled.

Urticaria and its cousin, angioneurotic edema, are largely anaphylactic manifestations, but evidence exists that no internal absorption of anaphylotoxins is possible without alimentary disease, however slight. For the most part constipation is present; at times mucous colitis (Highman and Michael).

Dermatoses Conceived to Be Due to or Associated with Diet

Intimately associated with alimentary disturbances is the relation of diet to dermatoses. Precisely as scarcely a skin disease has failed to be treated internally by catharsis, so is there scarcely one that has not been ascribed to dietetic indiscretion. It may be conceded without argument that food should be chewed properly, eaten deliberately at regular times, and simply prepared, and that a meal should represent a properly balanced mixture of proteid, carbohydrate, fat, fluid, vitamins and salts. Overeating and undereating are equally to be condemned. With less detail, the above might be summed up in the words "common sense," and included in this concept should be proper regard for the temperature and seasoning of food. But, aside from these factors, there are certain others more directly responsible for the causation of cutaneous reactions. The relation of proteids, whether animal or vegetable, to urticaria is universally admitted. Bulkley, years ago, considered psoriasis due to overindulgence in meat. The number of vegetarians with psoriasis amply discredits this belief. More recently, Schamberg and others have associated the disease with excess nitrogen ingestion, including that of leguminous sources—a much more scientific concept than Bulkley's. Even this cannot always be substantiated. The consensus of opinion is that diet plays a small rôle in producing psoriasis.

Eczema has also been ascribed to dietetic errors. The writings of Towle and Talbot, Freeman(*b*), Sturtevant, Charles White(*a*), and many others are examples. What applies to the relation of alimentary disease to eczema equally applies to diet in this connection. If eczema were often due to food, certainly we should readily find proof in the infantile form, for babies prevailingly get one food, milk. Nevertheless, in spite of an immense literature on the subject, pediatricians have proved nothing. One school thinks infantile eczema due to proteids, another to fats, another to carbohydrates. There could hardly be a fourth school of believers in the dietetic cause, unless they blamed whole milk, and what a delicious *re-*

ductio ad absurdum would be offered by attempting to remove milk from a baby's diet to destroy the eczema—or the baby. It is almost as ridiculous to blame any single ingredient of the milk when one reflects that there are as many schools as there are ingredients. In twelve years of observation, unhypnotized by the siren notes of the literature, one of us (Highman) has failed to see a single case of infantile eczema benefited, to say nothing of "cured," by modifying the diet of an afflicted baby. But the fact remains that most babies "outgrow" the eczema at about two years of age, or when they get a more liberal diet. This compels the conclusion that, after all, something in the milk diet is at fault, even though the fact remains unestablished.

If the difficulty is so great in infantile eczema, how much greater is it in adults to relate the disease to food, for so many more foods here come into consideration. The evidence is largely furnished by patients, and uncritically accepted as valid. Pickles cause it in one man, but cucumbers with vinegar do not; eggs in another, but not custard; steak in another, but not roast beef. And so it goes. It would look as if reason had been stampeded by superstition.

In urticaria, angioneurotic edema, and perhaps in prurigo, however, definite foods can often be demonstrated as the cause, as in Schloss' egg albumin cases, Smith's buckwheat case, and in our own series in which tomatoes, carrots, salmon, veal and other foods were incriminated. Prohibiting the food cures the disease.

Combining alimentary and dietetic causes may be considered the element in proteid putrefaction. Von Noorden(*j*) regards evidence such as the presence of ethereal sulphates in the urine insufficient but is interested in Lassar's observations on the use of yeast in furunculosis. Although yeast has been widely advocated as an intestinal antiseptic (Brocq, *La Presse médicale,* Vol. VII, No. 45, 1899, and others), the idea is fanciful, particularly when one regards the efficacy of vaccines, the alleged putrefaction remaining. Unna once used ichthyol for this purpose, and after Metchnikoff succeeded where Ponce de Leon failed, the civilized world gorged itself with lactic acid bacilli, and three more milestones in medical superstition were smilingly left behind.

Rosacea is provoked by foods that are too highly seasoned, or eaten at too high a temperature; by condiments, excess carbohydrate ingestion, tea and alcohol. Probably, in the last analysis, the underlying factor, as already indicated, is an organic disturbance, made worse by indiscreet eating. In a lesser degree the same applies to acne vulgaris, but the real cause of this disturbance is still unknown, and is more likely connected with the biological upheaval incidental to puberty itself.

No discussion of ingested poisons would be complete without reference to drug eruptions. Iodids, bromids, arsenic, mercury, phenolphthalein, copaiba, digitalis, morphin, quinin, antipyrin, and its associates, and

numerous other drugs, are capable of causing dermatoses. These are prevailingly erythematous or urticarial, but the first two provoke vesicular, pustular, and granulomatous lesions also, while quinin and arsenic may cause herpes, and the latter also a zosterform dermatosis.

To sum up, then, there is no experimental evidence that digestive diseases or faulty diet cause dermatoses, except with regard to urticaria and drug eruptions. What proof thereof exists is clinical, as in rosacea, psoriasis, and the fact that infantile eczema usually disappears spontaneously with the end of infancy, or when the milk intake is modified by a more varied diet. To find ethereal sulphates in the urine, undigested food, or too much starch in the stool, or gastric hyperacidity, gives circumstantial evidence which may not be proof at all, but merely coincidence. It is only in urticaria that we observe anything like cause and effect, while in rosacea we see something approximating it.

Dermatoses Conceived to be Due to or Associated with Cardiovascular Disease

The relationship between this group of diseases and dermatoses is vague. We may dismiss the petechiæ accompanying bacterial endocarditis with a word, for they are probably due to bacterial emboli, and it is the bacteremia, rather than the heart disturbance, that is responsible. But with chronic endocarditis, particularly during periods of decompensation, and irrespective of drug ingestion, toxic erythemas and even attacks of erythema nodosum may be noted. The incidence of these conditions has not been calculated, but the phenomenon is rare.

More directly connected with the theme are dermatoses due, in all likelihood, to disturbed vasodynamics in valvular disease. The simple picture of asphyxia is thus accounted for, and even chillblains, Raynaud's disease, and perhaps scleroderma may have a remotely related origin. Thrombophlebitis obliterans of Buerger, and other gangrenes are due primarily to actual vascular disease determining local necrosis.

Many of the telangiectasias are due to primary disease in the small skin capillaries. Angioma serpiginosum of Hutchinson and purpura annularis telangiectodes of Majocchi, are in this category. Histologically, an inflammatory or degenerative process is observed in the capillary walls; probably due to a systemic disease affecting the vessels in a manner analogous to Stokes' syphilitic telangiectasia.

The purpuras, scruvy, and pellagra may be mentioned in this connection, but in the final analysis either infection or intoxication is the determining factor, the vascular rôle being purely incidental.

On the whole, no work has been done in this particular field, and the diseases enumerated indicate possibilities, the significance of which

cannot be arbitrarily gauged. This subject merits extensive study, as it is quite likely that a deeper insight into these conditions would be no less valuable to alert internists than to dermatologists.

Dermatoses Conceived to be Due to or Associated with Renal Disease

This subject is too difficult to analyze in detail. The physiological balance between perspiration and urine is such that one would expect renal disturbances to involve the skin more frequently than apparently occurs. The subtler phenomena of the excretion of substances soluble in the urine, namely, the end products of metabolic waste, would apparently be related to many dermatoses. Thus, in the various forms of nephritis, one would fancy that the skin would exhibit numerous changes. This is not the case, though, except in the presumptive instances to be indicated below, in connection with disturbed nitrogen metabolism.

One condition, nevertheless, which clinically simulates prurigo, and which is associated with chronic nephritis, must be mentioned. It is not known, however, whether this is fact or only surmise, or with what type of nephritis it is prevailingly associated. Uremic patients often scratch themselves, but whether they really have a pruritus, or whether the scratching is a manifestation of lowered mentality, cannot be stated. If there is any connection between nephritis and cutaneous reactions, its expression must be most exceptional, for in hundreds of cases of kidney disease of this sort, one rarely finds a single instance of skin involvement.

In other renal diseases, such as hydro- and pyonephrosis, pyelitis, perinephric diseases, and the like, skin diseases have never been reported. Renal tumors cause none, but in other conditions a certain relationship appears to exist. Scarlatina scarcely is a fair example, for the nephritis appears long after the acute cutaneous phase of the disease has subsided. On the other hand, the more marked forms of arsphenamin and mercury dermatitis are at times associated with nephritis, sometimes hemorrhagic, and occasionally accompanied by uremia, while in bichlorid poisoning there may be cutaneous phenomena, with the well-known renal reaction.

Dermatoses Conceived to be Due to or Associated with Nervous Diseases

The relationship between the central and peripheral nervous system and cutaneous diseases is not definite, except in few instances, although it is surmised in many diseases of the cord, such as syringomyelia, Morvan's disease and tabes which produce well-known trophic ulcers, includ-

ing decubitus. The latter, however, is also the result of marasmus of any origin, and may be independent of central nerve lesions. Whether febrile diseases produce skin changes directly through intoxication, or through the intermediate influence of the central nervous system, is not known, but the hair falls, and the nails become horizontally ridged. Actual distortion of the nails is at times encountered in syringomyelia and Morvan's disease.

Peripheral nerve disturbances are associated with zoster, although the prominent lesion in zoster is in the ganglia on the posterior roots. Nevertheless, the neuralgia indicates a marked involvement of the nerve itself. Simple herpes may be the result of peripheral neuritis. Kreibich has written a monograph on the influence of the nervous system in producing erythemas, wheals, and bullæ. Injury to peripheral nerves at times causes a condition known as "glossy skin," which disappears when the nerve heals, as Paget pointed out. Alopecia areata has been regarded, albeit on an inconclusive basis, as the result of a peripheral neuritis.

Mental obliquity of various types and degrees of intensity is related to certain dermatoses. These are mainly self-inflicted lesions, as in hysterical mutilations; or are the result of habit, or mannerism, as the pulling of hairs, or the consistent scratching of definite areas. The lesions are so artificial in aspect, and so unlike other dermatoses, as immediately to arouse the observer's suspicions.

Dermatoses Conceived to be Due to or Associated with Respiratory Diseases

Excepting the polymorphous erythemas and purpuras associated by Osler with asthma, and the infantile eczemas that Czerny found accompanying the same condition, there would seem to be no relationship between the respiratory tract and the integument. Often nasal obstruction causes a dilation of the cutaneous veins of the nose, but this is purely mechanical—a vascular stasis due to an anatomical peculiarity.

Dermatoses Conceived to be Due to or Associated with Endocrin Disturbances

Myxedema and Graves' disease cause well-known changes in the skin and hair, so well-known, in fact, that further allusion to them is unnecessary here. In addition to these, it has appealed to the fancy of many to explain a wide range of dermatoses on the basis of ductless gland disturbances. Judgment must be withheld as to the soundness of views concerning the cutaneous expression of endocrin changes. That such a relation exists cannot be doubted. What it is, no one yet knows. To date

the field has been exploited rather than studied, and a gracious curtain of reserve may be allowed to descend until scientific footlights illuminate a worthier scene.

Our knowledge may be summed up very simply. We know that thyroid disease may cause a few cutaneous changes, well recognized for a generation or more. Hirsutes is at times associated with pituitary disturbances. Acanthosis nigricans is due to abdominal neoplasia which may derange the sympathetic system. Addison's disease is caused by lesions in the suprarenal gland. Nothing more can be asserted. Other than this, so far as the skin is concerned, endocrinology will still be more honored in the breach than in the observance.

Dermatoses Conceived to be Due to or Associated with Disturbed Nitrogen Metabolism

Disturbed nitrogen metabolism has been regarded as the cause of nearly every dermatosis, the etiology of which had not been otherwise conjectured—eczema, psoriasis, pemphigus, prurigo, the lichens—all have been referred to this origin. With this belief in mind, one of us (Highman) examined about forty cases of nephritis with hypertension, many of which were uremic, and except for an isolated case of pruritus, or prurigo, we have yet to see a single instance of renal disease with or without evidence of disturbed nitrogen balance, accompanied by a true dermatosis. This is significant, but not conclusive. There may be disturbances of nitrogen metabolism unaccompanied by renal disease, with a greater incidence of cutaneous involvement. Experience negates this, although the literature reflects the assumption, however unsupported by fact, either clinical or experimental.

Schamberg and Raiziss found no relationship between nitrogen disturbance and eczema, in two carefully studied cases. Johnston, on the other hand, found a disturbed nitrogen balance in psoriasis, urticaria, eczema, dermatitis herpetiformis and prurigo. The most constant change was a decrease in urea, and a corresponding increase in rest nitrogen. Tables accompany his studies. Arignac, quoted by Von Noorden, found the urea increased. Examples might be reduplicated, but there is no agreement in findings in any disease.

Perhaps psoriasis has received more study than any other dermatosis. Linser, in psoriasis and leucemic exfoliative dermatitis, found an increased albumin destruction where the patients were exposed to high temperatures (15 to 30 degrees centigrade) for eight days. In these diseases he found the surface temperature only one degree centigrade lower than the rectal, a phenomenon he ascribed to dilatation of the skin capillaries. Von Noorden quotes several writers who determined a great loss of nitrogen in the

psoriasis scales. Schamberg and his collaborators found that psoriatics stored nitrogen easily, and that very little of this substance was excreted in the urine, that a low nitrogen diet was beneficial, and that huge quantities of nitrogen were lost in the scales, and finally, that the retention of nitrogen was not registered in increased weight. In general, there is a widespread belief that restricted nitrogen intake is beneficial to psoriatics. The English dermatologists associate the disease with gout. There is no doubt that psoriasis is greatly influenced, for better or worse, by physiological crises in the patient. Thus, in some women, the disease improves or increases during pregnancy, lactation, or the menses, while in both sexes it gets better or worse during acute intercurrent illnesses. At times there is involution on a restricted nitrogen diet; at times the reverse is true. The conclusions to be drawn are so uncertain, the facts apparently so contradictory, that psoriasis may be regarded as a disease of probable metabolic origin, of which nothing further may be stated than the probability.

Dermatoses Conceived to be Due to or Associated with Carbohydrate Metabolism

There is some evidence that rosacea, acne, and many of the suppurations of the skin have an associated hyperglycemia. On the other hand, Pels did not find this to be the case, but rather that the blood sugar was increased in eczema and the erythemas. In diabetes, it is widely known that intertrigo, gangrenes, and a peculiar yellow, nodular disease, called diabetic xanthoma, arise. All of these conditions improve or disappear with the control of the underlying condition.

Dermatoses Conceived to be Due to or Associated with Miscellaneous Causes

Xanthoma tuberosum is associated with disturbed cholesterin metabolism, as Lebedew showed in a beautifully conducted piece of research. He fed cholesterin to rabbits and typical xanthoma lesions developed at sites traumatized by setons. Schwartz, Levine and Mahnken found a diminished alkali reserve in a wide range of unrelated dermatoses. This work could not be corroborated by Sweitzer and Michelson. Barber associated the seborrheas with acidosis in a very inclusive study. Severe illnesses cause dystrophies of the nails, as Heller(*c*) pointed out, although the fact is known to every internist. After severe febrile diseases horizontal ridging of the nails occurs. The hair also falls out.

This, then, is a résumé of the little that has been accumulated in the field in question. One thing is clear, namely, that a relationship exists

between the integument and the tissues it envelops. It is important to trace this relationship until the problems are elucidated. As Engman said, the skin is the mirror of the body. In the foregoing the value of the work done has been rather understated, in the hope of avoiding unwarranted enthusiasm. As a matter of fact, the application of the principles implied in the work reviewed makes for greater alertness in diagnosis, and for more efficacy in treatment, even though surmises rather than facts guide us. In addition to the foregoing, the more important dermatoses will be catalogued, accompanied by thumb-nail sketches of related general disturbances.

Acne or Acne Vulgaris.—This well-known pustular disease has been ascribed to the stormy metabolic disturbances inherent in the unfolding of puberty. More especially it has been ascribed to overindulgence in starchy food and sugar, and to carbohydrate indigestion, hyperglycemia (Schwartz, Highman and Mahnken), while Schamberg and Strickler found complement fixation possible between the serum of acne patients and bacterium coli used as antigen.

Acroasphyxia.—Cyanosis of the smaller extremities has been associated with organic heart disturbances, notably mitral disease, and with ordinary so-called vasomotor instability. As a forerunner of erythromelalgia, Raynaud's disease, and the various gangrenes, it is due to organic central nervous or vascular disease. It is an objective indication of predisposition to frostbite.

Dermatitis (The Simple Variety, Including Eczema).—This is a simple, acute, subacute, or chronic catarrh of the skin, caused by a wide variety of external agents, chemical, physical, infectious and, undoubtedly, often by internal disturbances, some of which are surmised, others not yet even remotely understood. For the most part nitrogen retention or some other type of disturbed nitrogen metabolism has been incriminated, but proof is still lacking, as is shown in earlier paragraphs.

Dermatitis Exfoliativa.—Arsenic poisoning can produce a general exfoliative dermatitis. Scarlatina terminates with a similar process. Thus it is argued that in the unexplained varieties of the group, the cause must be either infectious, or toxic, and in the second event, that the poison must be ingested, or manufactured in the body. The favorite belief, although entirely unsubstantiated, is that there is a disturbance of nitrogen metabolism.

Dermatitis Herpetiformis.—The remarks on the internal causation of eczema apply in this disease too.

Erythema Multiforme.—In some of its manifestations, particularly erythema nodosum, this disease is allied with acute rheumatism, but more with subacute. It is also considered anaphylactic, as urticaria, and one form of multiform erythema participates in the Osler syndrome. Many drug eruptions resemble multiform erythema, and the bullous

subvariety so closely simulates dermatitis herpetiformis that it is supposed to be the result of disturbed nitrogen metabolism.

Furunculosis.—Save for the factors incidental to puberty, the etiology of furunculosis is similar to that of acne. In addition, the disease is often caused by diabetes.

Gangrenes.—Many of the views applied to acroasphyxia equally apply to the gangrenes. Diabetes, syringomyelia, tabes, atherosclerosis, etc., to say nothing of the so-called spontaneous gangrenes of the skin, those due to self-mutilation (hysterical or insane subjects), gangrenous zoster, and varieties due to asthenia, as decubitus, indicate the tremendous range of causative possibilities in this condition. Biochemical, central nervous, vascular and trophic diseases are among the organic causes, while mental diseases are among the functional.

Pemphigus.—This disease in its different forms has been subjected to about the same series of explanations as eczema and dermatitis herpetiformis. The disease is invariably fatal, however, and behaves much more like an infectious syndrome than anything else.

Prurigo.—This disease is regarded by many as papular urticaria, in which event its etiology is that of the latter disease. (See below.) By others it is regarded as a metabolic disease provoked in a manner similar to dermatitis herpetiformis.

Prurigo lymphatica is a nodular disease of the skin found in lymphatic leucemia.

Psoriasis.—The greater part of the section on diseases due to disturbed nitrogen metabolism is devoted to psoriasis. There is no object in rewriting the passage.

Rosacea.—This disease is caused by chronic gastritis, and conditions producing the latter, such as alcoholism, hyperacidity, gastric ulcer, excessive use of condiments, overindulgence in carbohydrates, and in short all chronic alimentary disturbances. Gynecological diseases, including the disturbances of the menopause, may also be responsible. Everything stated of ordinary acne, except what relates to puberty, applies to rosacea.

Seborrhea.—Unless seborrhea is due to an undiscovered infection, the paragraphs on acne and rosacea are applicable.

Urticaria.—This condition, in part, is explicable in the same manner as multiform erythema. A great number of cases are due, however, to food sensitization, or sensitization to other alien proteids. Chronic forms, particularly those resembling prurigo, may be due to disturbed nitrogen metabolism. Thus the factors may be diet, anaphylaxis, biochemical derangements, and finally, still unsuspected causes. Contributory factors are food, organic or functional maladies of the alimentary tract, and parenteral exposure to proteids to which the patient is susceptible.

Xanthoma.—Xanthoma diabeticorum is due to diabetes, xanthoma tuberosum to disturbed fat metabolism.

The Metabolism in Diseases of the Neuromuscular System ..... ***Francis H. McCrudden***

The Supply of Glucose—Progressive Muscular Dystrophy—Creatinuria—Alkalosis—Hypocholesterinemia—Progressive Muscular Dystrophy as an Endocrine Disease—Progressive Muscular Atrophy—Myasthenia Gravis—Amyotonia Congenita.

Metabolism in Diseases of the Neuromuscular System

FRANCIS H. McCRUDDEN

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Microchemical methods have been devised by means of which, under special conditions, it is possible to demonstrate metabolism in an isolated active nerve. But in a sick patient we do not study the metabolism of an isolated nerve, or even of the whole nervous system alone; we study the metabolism of the body as a whole. And the quantities of energy and matter involved in the metabolism of the purely nervous activities alone are so very minute in comparison with the total metabolism of the body as a whole that it is not possible at present to recognize pathological changes in the metabolism of the nervous system in disease. All attempts to demonstrate either metabolic changes resulting from purely psychic or nervous activities, or metabolic changes in the nervous system in disease have given negative results (Gumprecht, Mott, Benedict(*a*), Donath, Folin and Shaffer, Luciani(*b*), Oppenheim, Schtscherbak, Singer and Goodbody, Speck).

But diseases of the nervous system may lead to changes in the metabolism of other organs.

All the activities of the body take place in response to stimuli. A stimulus may arise in one part of the body; the corresponding activity may take place in another part of the body. A slight stimulus may produce a profound reaction; a strong stimulus a slight reaction. A single stimulus may call forth several activities; numerous stimuli may result in a single response. A chemical stimulus may call forth a physical reaction; a mechanical stimulus may give rise to a chemical reaction. The end result is purposeful activity; the activities fulfill some useful function. This adaptation of responses to stimuli is brought about through the nervous system. All centripetal impulses pass to the nervous system, where they are coördinated into useful forms which then pass out to the various organs as a stream of controlling centrifugal impulses. It is such impulses that determine the nature and extent of all the activities of the organs.

The foregoing applies, not only to physical activities, such as muscular

contractions, but to metabolic activities as well. Thus, throughout a period of years, despite great variation in the rate of heat loss, and in the supply of fuel, the body temperature is constantly maintained at the optimum temperature for physiological activities; and with great and rapid variations in the supply of carbohydrate in the food, on the one hand, and in the rate of carbohydrate catabolism on the other, the blood continues to maintain an even level of one-tenth of one per cent sugar. The very complex activities of various organs and functions, whereby constancy in the body temperature and blood sugar is maintained, are coördinated through the nervous system.

The changes in the metabolism in diseases of the nervous system result from failure of coördination. Through failure to adapt activities to needs, the activities become purposeless. After certain changes in the nervous system, the maintenance of normal heat regulation, and normal sugar may fail. When physiological connection between the nervous system and voluntary muscle is broken by the administration of curare, a mammal will lose the power of maintaining its body temperature constant (Rochrig and Zuntz). Even after such a relatively simple operation as puncture of the floor of the fourth ventricle, hyperpyrexia and hyperglycemia may arise. Similarly, in the case of bone metabolism: the structure and composition of the bone is determined by the needs; the plates of concelli are laid down along the lines of stress and strain, and shift with change in these lines; and where through disuse the stresses and strains become very slight, rarefaction of the bone results. The centripetal impulses in this case result from the pulls on the muscular ridges and the pressure on the articulating surfaces of the joints. When the continuity of the arc for deep reflexes is broken, as in tabes and syringomyelia, there is a failure of coordination leading to the formation of structureless bone; the bone metabolism "runs wild" and gives rise to the "Charcot joints."

Pathological changes in the nervous system may then lead to disturbances in the metabolism of any organ, function or compound. Such disturbances may be discussed either as disease of the nervous system, or as disease of the organ, or function, or compound in question. Thus, in the case of Charcot joints, and glycosuria of nervous origin, we can discuss the metabolism in both cases under nervous disease; or we can discuss one under bone disease, and the other under carbohydrate metabolism. With the exception of disturbances in the metabolism of the muscles it is more satisfactory, however, to discuss such disturbances under disease of the organ, or function, or compound in question, and they are so discussed in this book. In the present state of our knowledge, it is more satisfactory to discuss the metabolism of diseases of the muscles, and of nervous diseases which involve muscular metabolism together, as disease of the neuromuscular system.

The Source of Energy for Muscular Contraction

When a muscle contracts and does work, the energy expended is derived largely from the oxidation of glucose to carbon dioxid and water.

This is one of the most important chemical reactions taking place in the body—more important in some respects than the hydrolytic cleavages involved in protein metabolism, for the latter do not involve energy changes—and it has been much studied in health and disease.

We do not know the cause of this reaction. It cannot be carried out artificially—that is, without the aid of living cells or products of living cells—at body temperature. It has been attributed to enzymes, but such enzymes must be different from the ordinary amylolytic, peptolytic, and lipolytic enzymes, for the hydrolytic cleavages caused by the latter do not involve energy changes. Though they do not know the cause of this reaction, physiologists are now in accord with regard to one important fact concerning it: *The reaction is determined by intrinsic factors—factors within the cell itself—and not by extrinsic factors.*

Three factors are involved in this reaction: (a) the oxygen supply; (b) the glucose supply; (c) the living cell itself.

THE OXYGEN SUPPLY

During the years 1866 to 1878 one of the fiercest polemics in the history of physiology raged over the question of the significance of the oxygen supply, most of the great physiologists of that time—Voit, Pflüger, Ludwig, Liebig, and others—taking part in it. The facts are now stressed in books on physiology and metabolism. Lusk(*f*), for example, in the very first part of his introductory chapter states, "... the respiration does not cause or regulate the metabolism. On the contrary, the metabolism regulates the respiration. *The metabolism of the tissues, through its oxygen requirement and its carbon dioxid production, changes the condition of the blood and thereby regulates the respiration. These distinctions are of fundamental importance.*" [1] And Krehl(*d*) devotes the very first paragraph of the first chapter, in his well known book, to pointing out that it is not true, as formerly believed, that the function of the organs depends upon the amount of material they receive from the blood, but upon the condition of the cells themselves. Von Noorden's(*h*) book on metabolism is equally explicit. "All foundations for the view that the O_2 consumption and CO_2 output, are dependent upon the number and functional capability of the erythrocytes, or upon the quantity and functional utility of the hemoglobin, has been entirely removed by the investigations just described, and the theory of Voit and Pflüger, according to which the cells of the

[1] The italics are Lusk's.

organism are the chief determining factors in the processes of combustion within the organism, has been confirmed" (von Noorden(*h*)).

These three books are cited, because, being probably the most widely read, popular books dealing with metabolism, physicians are presumably familiar with them. Yet misconception on this fundamental point is most widespread, and in the belief that the extent of oxidation is determined by the oxygen supply, many pathological conditions are attributed to imperfect or defective oxidation.

In the older textbooks physiological oxidation is sometimes compared with the blacksmith's fire, the lungs with the bellows; the intensity of the metabolism being attributed to the activity of the respiration. This comparison, though no longer appearing in these words, still appears in principle; it is the basis of the idea expressed in the hypothesis so frequently seen in our medical journals, the "condition is due to products of insufficient oxygen supply."

One of the best known examples of this hypothesis is the belief that gout and the "uric acid diathesis" are due to the accumulation of products of incomplete oxidation. According to this hypothesis, uric acid is the immediate antecedent of urea in the oxidation of protein in the body; urea is the normal end product, but when oxidation is deficient, part of the protein may be oxidized only to uric acid (Haig). Liebig expresses a common belief when he says that sufferers from uric-acid concretions, who go to the country, sometimes, as a result of the better oxygenation, develop concretions of oxalic acid instead; and that when these same individuals, as a result of exercise, absorb still more oxygen, the concretions are completely oxidized to carbon dioxid and water (Liebig). Animals that drink much water, according to Liebig, excrete less uric acid than others; the water keeps the sparingly soluble uric acid in solution, so that it becomes more completely oxidized to urea.

Many investigators have attributed symptoms in leukemia, chlorosis, and emphysema to the products of incomplete oxidation, believing that the symptoms result from decreased external or internal respiration respectively (Bartels, Jacubasch, Mosler and Korner, Sticker, Virchow(*a*)(*b*)). It is stated that the fat found in the parenchyma of organs in anemia is deposited because the oxygen supply to the organs is insufficient to burn the fat (Bauer, Frankel(*a*)). Another finding in anemia, an increase in the proportion of urinary sulphur excreted in the form of unoxidized, neutral sulphur, has been attributed to the imperfect supply of oxygen to the tissues (Rudenko, Salkowski(*b*), Schmidt, Schupfer e de Rossi(*b*)). Later investigations have not confirmed this finding (Stadthagen(*b*), Taylor, von Moraczewski(*d*)). The introduction of hypophosphites into medicine was due to the belief that phthisis is due to incomplete oxidation (Editorial). Phosphorus and its partly oxidized derivatives, the hypophosphites, were recommended in this disease in the belief

that they attract oxygen to the tissues. Nencki and Sieber believed that they could measure the oxidizing power of the body under different conditions, by determining the amount of benzol that can be oxidized in the body to phenol; and concluded, as a result of such experiments, that in leukemia there is a decreased power of oxidation (Nencki and Sieber). Lactic acid formation in animals, suffering from phosphorus poisoning, has been attributed to decreased oxidation resulting from the low heart rate. Insufficient oxygen supply has been held responsible for glycosuria (Araki(*b*)).

Examples might be multiplied, but these will suffice to illustrate the nature of the fallacy.

The source of the error is found in the writings of Lavoisier. In 1777 (Lavoisier) Lavoisier cited metabolism experiments which he had carried out on birds, to show that respiration results in a combination of the carbon of the blood with oxygen to form carbon dioxid, from which he concluded that the process is analogous to that which, two years previously, he had described as combustion. But in elaborating this theory twelve years later, he laid the foundation for future error (Seguin et Lavoisier (*a*)). In this communication he speaks of incomplete oxidation of digestive products as a possible cause of disease, and urges the use of purgatives to rid the body of such products; he attributes the fevers of hospitals and prisons to the insufficient oxidation resulting from the impure air. In the following year, he declared that the metabolism is more active, and, therefore, more heat is formed in cold climates because the cold air is denser than warm air, and a greater amount of oxygen per unit of volume comes in contact with the surface of the lung (Seguin et Lavoisier(*b*)).

But Lavoisier's writings contain also the germ of the truth. In his communication of 1789, he states that, in spite of what should be expected, experiments with guinea pigs demonstrated that these animals take up the same amount of oxygen, and give off the same amount of carbon dioxid, whether they breathe pure oxygen or a mixture of oxygen and nitrogen. Lavoisier was already, therefore, on the right track. By 1789, he had overcome the technical difficulties of constructing apparatus for carrying out metabolism studies even in man; [2] by 1791, one of his pupils, Seguin, had developed a method of measuring the amount of oxygen in a mixture of gases (measuring how much of the gas would combine with heated phosphorus) (Seguin); and another pupil, Hassenfratz, by showing that the temperature in the lungs is no higher than elsewhere in the body, had corrected the erroneous notion that the oxidation takes place in the lungs. It is highly probable, therefore, that Lavoisier might have

[2] In 1789 Lavoisier demonstrated this apparatus to the members of the Academy, and in his communication described certain features of it; he promised to publish later a detailed description. In 1790, he again promised to describe this apparatus. I have searched for this promised report in probable places, but have never been able to find it.

carried out experiments that would have anticipated a century of errors. But scientific work was soon interrupted by the French Revolution,[3] and Lavoisier himself was executed early in 1794.

In 1849, Regnault and Reiset, and in 1858, Müller, as a result of experiments similar to those of Lavoisier, again pointed out that the activity of the metabolism remains unaffected by the oxygen tension. In 1838, Müller(*a*) stated clearly that oxidation does not take place in the blood, but in the tissues; he believed, however, that the respiration is not the result, but the cause of oxidation. The facts regarding internal respiration were stated correctly by Vierordt in 1844. According to Vierordt, oxidation takes place in the tissues, the blood merely transports the oxygen to the tissues and the carbon dioxid away from the tissues. Experimental confirmation of these hypotheses was furnished in 1857 by L. Meyer. Meyer demonstrated that the blood transports both oxygen and carbon dioxid.[4] A further confirmation of this theory was furnished in 1863 by Panum, who showed that the amount of oxygen absorbed, and the amount of carbon dioxid given off is not affected by the great loss of transporting power for oxygen which results from severe hemorrhage. But these experiments seem to have made but little impression at the time. In the subsequent polemics, these writers are given little credit; Pflüger, indeed, in 1868 rejected Meyer's conclusion (Pflüger and Zuntz).

Almost inextricably involved with the incorrect theories regarding the cause of oxidation, was an incorrect theory concerning the place of oxidation. Oxidation was believed to take place, not in the tissues, but in the blood stream. It was the gradual accumulation of data, not in harmony with this latter belief, and indicating that oxidation takes place in the tissues, that led to a readjustment of the views regarding the cause of oxidation.

Voit in 1866, was probably the first to incline physiologists to the belief that respiration is not the cause of metabolism, but the result of the needs of the metabolism (Lossen(*a*), Pettenkofer and Voit). He pointed out that the carbon dioxid eliminated is independent of the ventilation of the lungs.[5] In 1868 he showed that neither by section of the vagus, formation of a pneumothorax nor by hemorrhage, whereby respiration is diminished, can the amount of oxygen taken up, or the amount of carbon dioxid given off, be influenced (Voit(*b*)). In 1869 he showed that in leukemia—a disease which was believed to lead to a diminished internal respiration[6]—neither the oxygen intake nor the carbon dioxid

[3] The memoirs of the French Academy for 1790 were not published until 1797. A new set starting with volume I began in that year. The intervening years are not represented. The Academy was suppressed in 1793.

[4] Twenty years before, by means of a mercury pump, G. Meyer had extracted carbon dioxid and oxygen from both arterial and venous blood.

[5] Confirmed also by later experiments (Voit(*e*), Lossen(*b*)).

[6] Salkowski(*a*) studied this problem, too, and could find no products of incomplete oxidation in the urine of patients with leukemia (Salkowski(*a*)).

output is affected (Pettenkofer and Voit(*c*)). In the same year Senator searched in vain for evidence of incomplete oxidation in dogs, cats, and rabbits with tightly bound thorax (Senator(*a*)). In 1870 and 1871, Voit discussed the whole subject at great length, and answered especially, the objections of Liebig who was teaching the old view (Pettenkofer and Voit (*e*), Voit(*f*)). All these points have since been taken up by more accurate methods, and it has been demonstrated that the gaseous exchange is not affected by any of the factors mentioned in the preceding paragraph (Finkler, Gurber(*a*), Jackson, Magnus-Levy(*a*), Lukjanon, Möller).

Hoppe-Seyler accepted the new theory almost from the beginning, but did not feel that the experimental proof was complete until 1878 (Takacs).

Pflüger, who at this time was working on the gasometry of the blood, vigorously opposed the new view (Pflüger(*a*)(*b*), Pflüger and Zuntz, Zuntz (*a*)). In 1868 he stated: "No one will deny at the present day that oxygen is continuously used up in the blood vessels," and described experiments of his own and similar ones by Schmidt in Liebig's laboratory, intended to demonstrate the presence in the blood, during suffocation, of products of incomplete oxidation (Pflüger(*d*)). He declared also that dyspnea is due to products of incomplete oxidation (Pflüger(*c*)).

But Pflüger soon changed his opinion; he disproved his earlier findings of products of incomplete combustion in the blood, and, in 1872, rejected the old hypothesis, going even so far as to assert that he had recognized and taught the correct theory, even before Voit (Pflüger(*e*)). In extra large type, on page 46 of this paper, occurs the following very important sentence which expresses the views of physiologists to-day: "Here lies (in the cell itself alone) the essential secret of the regulation of the oxygen used by the body; it is not determined by the blood pressure, the velocity of the blood stream, or the activity of the heart, or the activity of the respiration."

In 1875, both Voit(*g*) and Pflüger(*f*) complain that the view is not everywhere known and accepted; according to Voit, even Liebig still opposed it. But that the results are not everywhere ignored is shown by Voit's further complaint against those who say that they recognized and demonstrated the truth before he (Voit) did; he disputes especially Pflüger's priority claims.

During the years 1875 to 1878, a great many papers on respiration and metabolism appeared from Pflüger's laboratory (Finkler, Pflüger(*g*)(*h*)(*i*)(*j*)(*k*)(*l*)(*m*)(*n*)(*o*). Many of them are very long, and offer as evidence not only Pflüger's experiments, but an enormous amount of other evidence from all departments of biology. Pflüger's own experiments deal largely with measurements of the amount of metabolism under conditions of varying oxygen supply. The papers are polemic in character, and their influence on other physiologists is reflected in the gradual change in the nature of the discussion. The earlier

papers are devoted to demonstrating that the opponents of the new view are wrong. Pflüger(*f*) and also Stinzing opposed especially the contentions of Ludwig and his pupils (Ludwig and Schmidt), that the oxidation in the muscles is proportional to the velocity of the blood, and that during suffocation the blood contains products of incomplete oxidation. He seems to have overcome opposition to the new view toward the end of this period, for later papers (Pflüger(*p*)(*r*)) are directed largely at those—in Hoppe-Seyler's laboratory especially (Takacs)—who dispute claims for priority.

With the opening of his new Institute in 1878, Pflüger seems to have concluded his work on respiration and turned his attention to other problems. Judging by a statement from Hoppe-Seyler's laboratory in 1878, the new view seems to have gained general acceptance at this time. Ludwig, however, remained unconvinced, and maintained his stand up to 1895, the year of his death (Lusk(*f*)).

It is difficult to determine precisely who should be given credit for teaching us the truth regarding this matter. The question of the cause of oxidation and that of the place of oxidation—though two separate questions—are not clearly separated in the early discussions. And the question arises, moreover, not only: who first taught the truth as a matter of belief? but also: who first experimentally established the facts upon which the truth could be based? Physiologists commonly give Pflüger credit for first demonstrating the truth regarding oxidation. As a matter of fact Voit first taught the truth; but Pflüger overcame opposition and convinced the scientific world. But the echoes of the fierce polemics of the '70's over these questions have not yet wholly died out.[7]

Though the facts in this important controversy were determined to the satisfaction of physiologists over forty years ago, and the controversy came to an end, the truth is not as widely known as it should be. Not only in the lay press, where we learn regarding the relations between "correct breathing," and the "laws of health" that "deep breathing is advisable in cold weather, because deep breathing stimulates the metabolism and thereby develops heat;" but also in the very recent medical journals, we find reference to the production of products of incomplete oxidation in heart disease (Peabody(*c*)(*d*)(*e*)(*f*), Pike), asthma (Zugsmith and Kahn(*b*)), arteriosclerosis (Barille), and shell shock (Cannon(*d*)).

Briefly stated, the facts are that to do a certain amount of work, or to develop a certain amount of heat involves the expenditure of a definite quantity of energy, and this requires the oxidation of certain amounts of carbohydrate, protein and fat. The volume of oxygen used up, and the volume of carbon dioxid formed in the oxidation of these foodstuffs are

[7] One of Voit's pupils has recently assigned 1877 as the date of Pflüger's recognition of the truth (Lusk(*a*)), whereas Pflüger(*e*) was disputing claims of priority with Voit as early as 1872.

fixed quantities determined by the amounts of carbohydrate, protein, and fat oxidized. A diminution in the oxygen supply, resulting from asthma, heart disease, anemia, and similar conditions, does not affect the oxygen consumption, or carbon dioxid production required to develop a certain amount of energy. If the work is done, the gaseous exchange is unaffected.

The result of a restriction in the oxygen supply is a diminution of the amount of work that can be done. The striking symptom, common to asthma, heart disease, anemia, high altitude sickness, and similar conditions, is weakness. The food supply in these conditions may be adequate to supply abundant energy, but the amount of food that can be utilized is limited to that which can be oxidized to carbon dioxid and water, by the oxygen available; and the oxygen available may be subnormal in quantity.

THE SUPPLY OF GLUCOSE

The same symptom, namely, muscular weakness, may result when the food supply is inadequate, or when, though adequate, the muscles cannot make use of it. Abstinence from food, in so far as its effect on muscular activity is concerned, is analogous to the inadequate oxygen supply resulting from diminished external or internal respiration. But weakness becomes a prominent symptom of starvation only when the starvation is rather extreme. Up to this point, compensatory processes—mobilization and transformation of material within the body—maintain the immediate source of muscular energy, blood sugar, at the normal level.

But muscular weakness is a prominent symptom when the food supply though adequate, cannot be utilized by the muscles. This is the case in the paralyses resulting from pathological conditions in the central nervous system and in curare poisoning. The food supply and the blood sugar may be normal, but the muscles cannot utilize these materials to do mechanical work. In severe diabetes the weakness is due to the inability of the tissues to oxidize glucose. In phlorizin diabetes, and in certain myopathies, the weakness is due to disturbances of the carbohydrate metabolism, resulting in inadequacy in the supply of the most immediate available source of energy—the blood sugar. Diabetes is discussed elsewhere in this work, but the other conditions come within the scope of this article.

Actively contracting muscle rapidly uses up glucose from the blood passing through it. A contracting muscle may use up more than six times as much as a resting muscle (Morat et Dufourt). The venous blood leaving a faradized muscle may contain only half as much glucose as the blood leaving a resting muscle (Quinquaud). Following severe muscular activity, the amount of glucose used may be so great that the blood sugar content of even the general circulation may fall (Broslauer, Chauveau et Kaufman(*b*)). Weiland, using a Gärtner ergostat, had six of his colleagues do severe muscular work, almost to the point of exhaustion, and

determined the glucose content of the blood before and after the work (Weiland(*a*)). There was a decrease in the glucose content of the blood in every case; the average blood sugar before exercise was 0.090 per cent, the average after exercise 0.065 per cent. The severe convulsions of tetanus may require so much glucose as to result in a fall of blood sugar in the general circulation to one-third the normal (Grote, Pnrjesz, Underhill and Blatherwick).

As the concentration of sugar in the blood falls, the muscular power diminishes, but it can be restored by glucose (Furth and Schwarz). Shumberg has demonstrated that the injection of carbohydrates enables fatigued muscle to contract more powerfully. This has been brought out in another way by Lee and Harrold, who observed that the intense fatigue shown by the muscles of the cat, whose blood sugar had been lowered by phlorizin administration, is not observed in control animals whose body has been flooded with sugar previous to the phlorizin administration. Hellsten has reported in man an increased capacity for mechanical work in the morning, before breakfast, twenty to forty minutes after ingesting sugar.

The gradual destruction of glucose by contracting muscle, and the power of glucose to restore activity to the muscle which has become enfeebled as a result of the disappearance of its store of glucose, has been demonstrated especially convincingly in the case of heart muscle. The heart may be isolated from the body, and, by perfusing with Ringer's solution, kept alive and contracting. As its store of glycogen becomes used up, the heart will beat more and more feebly, until it finally stops beating altogether. But if glucose is added to the perfusion fluid, this sugar is utilized (Locke and Rosenheim(*a*)(*b*)) and the heart beats more powerfully and for a longer time (Locke(*a*)(*b*)(*c*)). The isolated dog's heart, for example, uses up about 4 mgm. glucose per hour per gram heart muscle (Knowlton and Starling). In the case of the rabbit, the amount used from 1.2 to 1.7 mgm. glucose per hour per gram of heart muscle—about one-sixth per cent per hour of the heart weight (Locke and Rosenheim(*b*)). The utilization of glucose by muscle is a complicated physiological process. If the pancreas of the animal is extirpated before the heart is removed, the heart loses its power to utilize glucose (Knowlton and Starling); but this power can be restored by addition of pancreas extract to the perfusion fluid. This property is inherent in glucose alone; other sugars are impotent (Locke and Rosenheim(*a*)).

In man the blood normally contains about one-tenth of one per cent of glucose, the extremes in health and in disease in which the carbohydrate metabolism is not affected, being about 0.09 per cent and 0.12 per cent.

Table 1 and Chart 1 show the figures obtained by Weston, and McCrudden and Sargent(*b*) in health and various diseases. Other figures, differing only very slightly from these, are on record in the literature; but these investigators used the same technic which has been used in determining

the blood sugar in the pathological conditions we shall discuss in this chapter.

TABLE 1

Chronic Arthritis

(1)	0.086	(9)	0.109	(17)	0.103	(20)	0.110
(2)	0.088	(10)	0.115	(18)	0.105	(21)	0.127
(3)	0.090	(11)	0.118	(19)	0.107		
(4)	0.098	(12)	0.121				
(5)	0.101	(13)	0.124				
(6)	0.103	(14)	0.128				
(7)	0.104	(15)	0.131				
(8)	0.106	(16)	0.166				

Chronic Endocarditis

Chronic Nephritis

(22)	0.123	(25)	0.146
(23)	0.123	(26)	0.159
(24)	0.133	(27)	0.204

Miscellaneous Conditions

(28)	Psoriasis	0.090
(29)	Pernicious vomiting	0.094
(30)	Tuberculosis of spine	0.103
(31)	Multiple sclerosis	0.110
(32)	Neoplasm	0.118
(33)	Hypertension	0.120
(34)	Tumor of the cord	0.140
(35)	Hypotension	0.144

Normal

(36)	0.115	(37)	0.129

Manic-depressive Insanity

(1)	0.103	(6)	0.123	(11)	0.101	(14)	0.118
(2)	0.113	(7)	0.123	(12)	0.108	(15)	0.123
(3)	0.115	(8)	0.123	(13)	0.113	(16)	0.130
(4)	0.120	(9)	0.138				
(5)	0.120	(10)	0.140				

Epilepsy

Imbecility

(17)	0.097	(22)	0.123
(18)	0.115	(23)	0.126
(19)	0.120	(24)	0.138
(20)	0.120	(25)	0.142
(21)	0.122		

General Paralysis of the Insane

(26)	0.097	(36)	0.113	(46)	0.074	(56)	0.099
(27)	0.097	(37)	0.114	(47)	0.088	(57)	0.107
(28)	0.103	(38)	0.115	(48)	0.090	(58)	0.108
(29)	0.104	(39)	0.115	(49)	0.091	(59)	0.110
(30)	0.106	(40)	0.118	(50)	0.091	(60)	0.118
(31)	0.106	(41)	0.120	(51)	0.093	(61)	0.118
(32)	0.108	(42)	0.123	(52)	0.097	(62)	0.118
(33)	0.108	(43)	0.125	(53)	0.097	(63)	0.125
(34)	0.110	(44)	0.140	(54)	0.097	(64)	0.139
(35)	0.111	(45)	0.140	(55)	0.097	(65)	0.145

Dementia Praecox

Under similar conditions the amount of glucose in the blood of an individual seems to be very constant from day to day. Thus the amount in the blood of three individuals, a, b, and c at different times was as follows:

(a) Jan. 3, *0.145 per cent* July 5, *0.147 per cent.*
(b) Aug. 20, *0.159 per cent* Aug. 23, *0.159 per cent.*
(c) Dec. 17, *0.095 per cent* Dec. 30, *0.092 per cent.*

This concentration of blood sugar—one tenth of one per cent—is stubbornly maintained throughout prolonged starvation, almost up to death Allen(*a*)). This is to be attributed to the tenacity with which the organs maintain a glycogen reserve. After fasting twelve days and excreting large amounts of sugar in the urine, as a result of phlorizin injection, the body still contains glycogen(Prausnitz). Even after seventy-three days' starvation, glycogen is still found in the body (Pflüger(*s*)). The heart is known to maintain its normal glycogen content after fifteen days of starvation (Jensen, Kulz(*d*)).

Under normal conditions the blood sugar in the general circulation does not diminish to any great extent as a result of muscular activity, the normal level of approximately one-tenth of one per cent being maintained by the influx of glucose derived from the glycogen stored in the body, and from the carbohydrate (and carbohydrate-forming substances) in the food. As glucose passes into the blood stream from the gastro-intestinal tract, the concentration of glucose in the blood rises. But the rise is not very great, scarcely ever to above 0.12 per cent; the excess is quickly changed to glycogen and stored, chiefly in the liver, to a less extent in the muscles and other organs. There are then two opposing tendencies: one, muscular activity tending to diminish the concentration of blood sugar; and the other, the absorption of glucose from the gastro-intestinal tract, tending to increase the blood sugar. Standing between these two opposing tendencies, as a buffer to prevent any wide deviation of the glucose of the blood from the normal of one-tenth per cent, is the glycogenesis-glycogenolysis mechanism.

Many organs take part in controlling the concentration of sugar in the blood: the liver, muscles, pancreas, kidney, nervous system, adrenals and other organs of internal secretion. And the blood sugar can be altered by pathological changes in these organs. The immediate supply of blood glucose is provided chiefly by the glycogen stored in the liver. If the liver is poisoned by phosphorus its power to store glycogen becomes damaged, and the concentration of glucose in the blood may fall. Adrenalin has something to do with regulating the blood sugar concentration. Blood sugar may be increased by injection of adrenalin; the adrenalin increases the rate of glycogenolysis in the liver. Conversely, when the adrenals are damaged or removed, the glycogenesis-glycogenolysis functions of the liver become damaged and the blood sugar falls. The thyroid and pituitary glands have some similar relationship to these liver functions; administration of thyroid or pituitary gland increases the blood sugar; and after thyroidectomy the capacity of the heart to utilize glucose is diminished

(McLean). The parathyroids, too, are in some way involved in the process; after removal of the parathyroids, adrenalin administration no longer causes glycosuria (Mathews). These functions are indirectly under the control of the nervous system, and damage to the floor of the fourth ventricle, or severing the nervous connections of the adrenals or liver may lead to abnormal alteration in the blood sugar concentration. The pancreas furnishes some product that enables the muscle to oxidize sugar; and in pancreatic disease the absence of this substance may result in hyperglycemia. The kidney regulates the upper limit of blood sugar concentration, by eliminating glucose in the urine—in diabetes, e. g.—when the concentration in the blood reaches a certain level. Under the influence of phlorizin this threshold may be so greatly lowered as to result in glycosuria without hyperglycemia.

One symptom common to all conditions of hypoglycemia is great muscular weakness.

In three cases of Addison's disease—a condition characterized by profound prostration—quantitative determination of the glucose content of the blood by Porges(*b*) showed 0.052 per cent, 0.033 per cent, and 0.067 per cent—all very low results. These findings have been confirmed in other cases of Addison's disease (Bernstein(*b*), Shirokauer(*a*), Rolly and Opperman(*a*)).

Porges followed this point further in experiments on animals. He removed the adrenals from several dogs and compared the glucose content before and after the operation. There was a decrease in the glucose content of the blood in every case. His figures are shown in Table 2. Mayer(*c*) and Bierry and Malloizel had previously reported a fall in the blood sugar contents of cats after removal of the adrenals.

TABLE 2

GLUCOSE CONTENT OF BLOOD BEFORE AND AFTER REMOVAL OF ADRENALS

	Per Cent Before	Per Cent After
Dog 1	0.258 0.103	0.0058 0.0057
Dog 2	0.120	0.033
Dog 3	0.084	0.066
Dog 4	0.092	0.044

This association of fall of blood sugar content, with muscular asthenia and decrease in adrenalin, is quite in harmony with the fact previously observed by Batteli and Boatti and by Schur and Wiesel(*b*) that the epinephrin content of the blood of dogs decreases when these animals are made to undergo exhausting work on a treadmill.

An association between muscular asthenia and hypoglycemia has been noted in dyspituitrism and in atrophied babies. In Cushing's book on the

hypophysis, there is a case history of a man suffering from dyspituitrism, showing marked muscular asthenia and low blood sugar (0.039 and 0.053 per cent in two determinations) (Cushing(*b*)) Forshbach and Severin have reported nine such cases. Frank(*a*) observed in three atrophied babies 0.046, 0.040 and 0.050 per cent glucose respectively (0.10 to 0.11 per cent is the average figure for normal babies).

This same association of profound asthenia and hypoglycemia has been observed also after diphtheria poisoning (Rosenthal(*b*)), phosphorus poisoning (Frank(*b*)), hydrazin poisoning (Underhill(*a*)), thyroidectomy and parathyroidectomy (Janney and Isaacson(*a*)(*b*)), in myxedema (Gyelin), and in cretinism (Janney, Goodhart and Isaacson).

After thyroparathyroidectomy (Underhill and Blatherwick), adrenalectomy (Kahn and Starkenstein, Mackenzie, Porges(*b*), Schwartz(*a*)(*b*)), diphtheria toxemia (Rosenthal(*b*)), phosphorus poisoning (Frank and Isaac(*b*), Kaufholz, Mohr(*d*), Porges(*c*)) and hydrazin poisoning (Underhill(*a*)(*b*)), the liver and muscles have been found to contain far less than the normal quantity of glycogen. The low glycogen content of the organs in these cases is due to an impairment in the glycogen forming function. The carbohydrate ingested is not converted into glycogen (Porges(*c*) Frank and Isaac(*b*)). The liver of the adrenalectomized animal, for example, does not store any glycogen even when glucose enough is ingested to increase the blood sugar fivefold (Mackenzie). For a time at least, the extra glucose simply remains in the blood (Janney and Isaacson(*a*), Rosenthal(*b*), Underhill and Hogan, Frank and Isaac(*b*)); what happens to it finally will be taken up later.

It is evident that hypoglycemia is an indication of a profound defect in the carbohydrate metabolism. And, considering the evidence connecting glucose supply and muscular activity, it seems very probable that this deficiency in available carbohydrate can be held responsible for the muscular weakness in these conditions. This probability is much strengthened by the fact that in phosphorus poisoning and in diphtheria toxemia there is a definite parallelism between the severity of the myasthenia and the degree of hypoglycemia (Frank and Isaac(*b*), Rosenthal(*b*)) and that in successfully treated Addison's disease a definite parallelism has been observed between increase in strength and rise in blood sugar (Grote).

Progressive Muscular Dystrophy

Hypoglycemia and other evidence of abnormal carbohydrate metabolism in progressive muscular dystrophy were first reported in 1916 by McCrudden and Sargent(*a*), who observed that the muscular asthenia in this condition runs parallel with the degree of hypoglycemia, and who suggested that the disease is due to a disturbance of one or more of the

TABLE 3

BLOOD SUGAR IN CASES OF PROGRESSIVE MUSCULAR DYSTROPHY

	Per Cent Glucose in the Blood
1	0.064
2	0.080
3	0.068
4	0.086
5	0.065
6	0.070
7	0.080
8	0.067
9	0.080
10	0.085
11	0.073
12	0.068

internal secretions. The presence of hypoglycemia in this disease has since been confirmed by the same investigators (McCrudden and Sargent(*b*)) and by Janney, Goodhart and Isaacson; 12 cases in all have been reported.

Table 3 shows the amount of blood sugar found in these cases of muscular dystrophy (the first three cases reported by McCrudden and Sargent(*b*), the last nine by Janney, Goodhart and Isaacson).[1]

Chart 1 shows how these amounts of blood sugar compare with the normal.

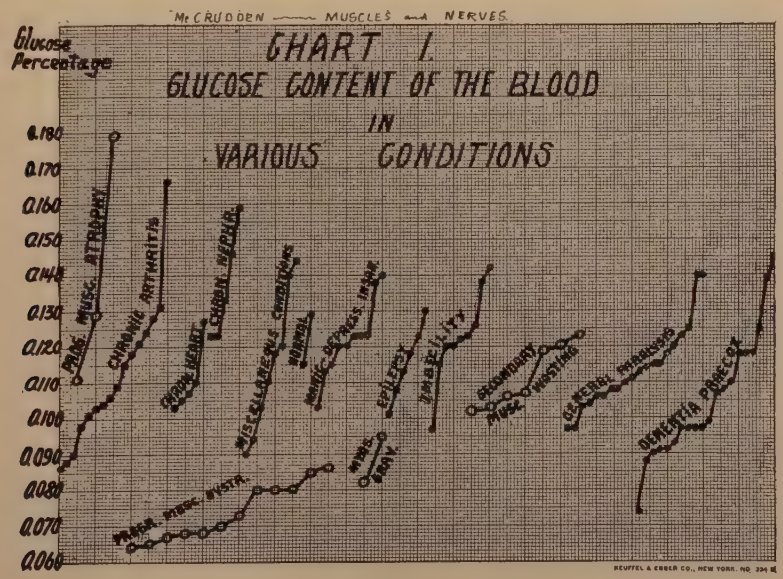


Chart 1.

The hypoglycemia in these cases is not secondary to the muscular wasting; it is not due to a lowered need of glucose by wasting muscles. If mus-

[1] As this book goes to press Brock and Kay report one more case, and Gibson, Martin, and Buell six out of nine cases with low blood sugar.

cular wasting could lead to hypoglycemia, then we should find low blood sugar in certain cases of rapidly progressing chronic arthritis, in which extensive and rapid muscular wasting is a prominent symptom. Table 4 shows the blood sugar in seven cases of generalized muscular atrophy, accompanying chronic arthritis (the first two reported by McCrudden and Sargent(*a*), the last five by Janney, Goodhart and Isaacson).

TABLE 4

SHOWING NORMAL BLOOD SUGAR IN MUSCULAR ATROPHY SECONDARY TO CHRONIC ARTHRITIS

	Blood Sugar Percentage
1	0.119
2	0.120
3	0.103
4	0.123
5	0.107
6	0.102
7	0.106

An observation made in one of the cases reported by McCrudden and Sargent(*a*)(*b*) that emphasizes strongly the relationship of myasthenia to the low blood sugar, is the parallelism between increase in muscular strength and rise in blood sugar. When first seen the patient was very weak, and for a long time had been able to walk, even with the aid of a walking stick, only clumsily and with difficulty, for a short distance. Administration of adrenalin and pituitrin, suggested by Dr. Spear of Boston as a means of mobilizing glycogen, was followed by rapid and marked improvement. He was eventually able, without the use of a cane, to climb the highest hill in Boston, on a winter day when the ground was in such bad condition, from rough ice and snow, that walking was exceptionally difficult. The patient was last seen about three and one-half years after improvement began, the improvement appeared to be permanent.

The figures for blood sugar follow:

TABLE 5

SHOWING PARALLELISM BETWEEN IMPROVEMENT IN STRENGTH AND RISE IN BLOOD SUGAR IN CASE OF PROGRESSIVE MUSCULAR DYSTROPHY

Oct. 27, 1915		0.068
Nov. 5, 1915		0.060
Treatment begun		
Nov. 16, 1915	Steady improvement in strength.	0.074
Nov. 23, 1915		0.091
Nov. 30, 1915		0.081
Feb. 21, 1916		0.095
June 20, 1916		0.110
March 7, 1917		0.103

At this point it may be well to advise caution in administering glucose intravenously in these cases. Underhill(*a*) administered glucose intra-

venously to three dogs showing hypoglycemia as a result of hydrazin poisoning, and the animals all died.

Hypoglycemia is not the only evidence of disturbed carbohydrate metabolism that has been observed in progressive muscular dystrophy. Besides hypoglycemia there is:

(1) Creatinurea.
(2) A hypocholesterinemia.
(3) A delayed glucose utilization.

Creatinuria.—Large quantities of creatin are constantly present in the urine of these patients with progressive muscular dystrophy. Table 6 shows the amounts found per day in sixteen cases (the first five reported by Levene and Kristeller(*a*), the next two by McCrudden and Sargent(*a*) (*b*), the last nine by Janney, Goodhart, and Isaacson).[2]

TABLE 6

AMOUNT OF URINARY CREATIN PER DAY IN PROGRESSIVE MUSCULAR DYSTROPHY

	Number of Days Urine Examined	Average Amount of Creatin per Day in Grams
1	7	0.465
2	11	0.503
3	4	0.175
4	3	0.264
5	3	0.621
6	3	0.600
7	3	0.610
8	3	0.528
9	3	0.525
10	3	0.172
11	3	0.636

Traces of creatin have been reported occasionally in the urine of apparently normal women, and creatin occurs in the urine of normal children. But creatin does not occur in the urine of normal men. It has been found in the urine in man in diabetes, in starvation (Benedict(*b*)) and when carbohydrate is withheld from the diet. That there is a relationship of some sort between carbohydrate metabolism and creatinuria was first pointed out by Cathcart(*b*). This feature has been further studied by Mendel and Rose, who showed that creatin disappears from the urine in these cases when carbohydrate is administered; neither protein nor fat can replace the carbohydrate in this respect. In dogs, creatinuria accompanies hydrazin poisoning (Underhill and Kleiner) and phlorizin poisoning (Underhill and Bauman(*a*)), both of these conditions accompanied by hypoglycemia. In the rabbit, an animal in which hypoglycemia does not always follow hydrazin poisoning, creatinuria occurs only in those cases in which hypoglycemia does follow (Macadam(*b*)). The con-

[2] As this book goes to press Brock and Kay report one more case, and Gibson, Martin, and Buell nine cases, all of them showing creatinuria. Gibson and Martin find that ingested creatin is promptly and completely eliminated in this disease.

nection between carbohydrate metabolism and creatinuria is so close that, when we find creatin in the urine of a man, we suspect something abnormal in the carbohydrate metabolism; we suspect that glucose is not being oxidized in sufficient quantities.

The urinary creatinin was very low in all the cases reported by Janney, Goodhart, and Isaacson, and Gibson, Martin and Buell, but not in those reported by McCrudden. The decreased excretion of creatinin is not particularly significant. The amount of urinary creatinin is an indication of the muscular efficiency of the patient (Shaffer (*a*)). A low urinary creatinin is found in other conditions accompanied by muscular asthenia, and in progressive muscular dystrophy is probably secondary to the myasthenia.

Alkalosis. The possibility that alkalosis plays a part in the etiology of progressive muscular dystrophy was suggested by the following facts connecting alkalosis, hypoglycemia, and creatinuria:

(A) *Alkalosis and Hypoglycemia.*—(a) Alkali administration causes hypoglycemia (Underhill(*e*) Elias); it diminishes and may even prevent epinephrin-hyperglycemia and glycosuria (Elias, McDanell and Underhill(*e*)).

(b) Acid administration increases glycogenolysis, causes hyperglycemia and augments epinephrin hyperglycemia (Elias).

(c) The hypoglycemia induced by injection of guanidin hydrochlorid is preceded by severe acidosis and the two are correlated (Watanabe(*a*) (*b*)(*c*)).

(d) If a frog be kept in a slightly acid solution, its store of glycogen diminishes; if in an alkaline solution, the glycogen store augments (Erhlich).

(e) A base-forming diet is more efficient as a glycogen former (McDanell and Underhill(*d*)) and gives a greater epinephrin glycosuria (McDanell and Underhill (*b*)) than an acid-forming diet.

(f) Epinephrin hyperglycemia is accompanied by a decrease (Peters and Geyelin) and thyroparathyroidectomy hypoglycemia by an increase in the alkali reserve of the blood (Wilson, Stearns and Janney, Wilson, Stearns and Thurlow).

(B) *Alkalosis and Creatinuria.*—(a) In rabbits creatinuria follows administration of acid or an acid diet (Underhill(*e*)) in which case the urine is always acid (Underhill and Bogart).

(b) Alkali administration diminishes, and sometimes abolishes the creatinuria of starvation (Underhill(*d*)).

But alteration in the acid base equilibrium severe enough to produce hypoglycemia leads to marked changes in the reaction of the urine (McDanell and Underhill(*a*)), and such changes are not present in progressive muscular dystrophy. Ammonia excretion is normal, never higher than 0.43 gram per day in the cases reported by McCrudden and Sargent(*b*)

and acetone and diacetic acid are not present in the urine (McCrudden and Sargent(*a*)).

Hypocholesterinemia.—The cholesterin of the blood in three cases of progressive muscular dystrophy was:

Case 1. 0.50-1.44 mg. per 100 grams blood,
Case 2. 1.18 mg. per 100 grams blood,
Case 3. 1.40 mg. per 100 grams blood.

By the same method, the amount in normal blood runs from 1.60 to 2.40 mg. per 100 grams blood and averages about 1.90 mg. (McCrudden and Sargent(*b*)).

Hypocholesterinemia alone does not indicate any abnormality in the carbohydrate metabolism; the amount of cholesterin in the blood does not run parallel with the amount of glucose (McCrudden and Sargent(*c*)). But, taken together, with the fact that hypercholesterinemia accompanies the hyperglycemia of diabetes (Bloor(*c*), Joslin, Bloor and Gray), the association of hypocholesterinemia with the hypoglycemia of progressive muscular dystrophy is certainly suggestive. In this connection it is of significance to note that in the case which showed such marked improvement, followed by McCrudden and Sargent(*a*), the cholesterin content of the blood increased with the improvement in strength and the rise in blood sugar. The amount rose rapidly to 0.177 per cent and later to 0.211 per cent, both of these normal figures.

Delayed Glucose Utilization.—It has been observed by Janney that the administration of 1.75 grams of glucose per kilogram body weight in forty per cent solution causes a rise in the blood sugar in normal individuals of about twenty per cent, followed by a return to normal after one and one-half to two hours; glycosuria does not occur. This is the glucose tolerance test, the details of which were first worked out by Hamman and Hirschman. The results have since been confirmed by other observers (Rohdenberg, Berhard, and Krehbiel). According to Janney, Goodhart, and Isaacson, the result of this test in cases of progressive muscular dystrophy is different in three respects:[3]

(1) The percentage rise is greater than in the normal. In nine cases studied, the increase in blood sugar averaged 65 per cent as compared with 20 per cent in normal cases. But on account of the lower base level of blood sugar concentration from which the rise starts, the absolute level attained is generally no higher than the level attained normally.

(2) In five out of nine cases which they studied, there was a distinct delay in the disappearance of carbohydrate from the blood. Instead of a fall in the blood sugar to normal before the end of the second hour after glucose ingestion, the normal value was not reached until the end of the fourth or fifth hour after ingestion.

[3] Confirmed recently by Brock and Kay and by Gibson, Martin, and Buell.

(3) Glycosuria followed in five out of nine cases.

A similar delay in glucose utilization has been observed by Janney and Isaacson(*b*) accompanying the hypoglycemia in thyroidectomized dogs. And Rosenthal(*b*) has observed that hypoglycemia accompanies diphtheria toxemia in rabbits, except following administration of glucose, when a hyperglycemia greater than that possible in normal animals occurs. The liver and other organs appear unable to change the sugar to glycogen in the normal manner.

Impaired Glycogenesis.—Hypoglycemia can be brought about by a lowered threshold value for excretion of glucose through the kidneys—renal diabetes. Thus the sugar content of the blood can be lowered by the administration of phlorizin, a drug which increases the permeability of the kidney for glucose and causes glycosuria. The absence of glycosuria in cases of progressive muscular dystrophy excludes this as a possible cause of the hypoglycemia (McCrudden(*g*), McCrudden and Sargent(*a*)(*b*)).

As glucose passes from the blood into the muscles and other tissues where it is to be oxidized, the loss is made good from the glycogen store of the liver. Replenishment is rapid and quantitative, the blood sugar being thereby maintained at a fixed level. Hypoglycemia can result only from a failure of replenishment to keep pace with the needs, a loss of balance between supply and demand.

Increased needs may result from increased sugar utilization or from loss through the kidneys—renal diabetes. In progressive muscular dystrophy we can rule out both. There is neither the rise in temperature nor the increase in heat loss that would accompany increased sugar catabolism (McCrudden(*g*)). And the fact that the urine is sugar free (McCrudden and Sargent(*a*)(*b*)) rules out renal diabetes.

It has been pointed out earlier in this article that all forms of experimental hypoglycemia are accompanied by an impairment in the glycogen forming capacity of the liver and muscles. In these cases the glycogen content of the liver and muscles is much below normal. It seems probable that the immediate cause of the hypoglycemia is to be looked for in a decreased rate of replenishment, consequent on the diminished glycogen reserve.

The possibility that the hypoglycemia in progressive muscular dystrophy might be due to impairment of the glycogen-storing power, led McCrudden and Sargent(*a*) to determine the glucose content of the blood in one of these cases after a short period of starvation. Normally, as fast as the glucose of the blood disappears, a continuous new supply, resulting from the glycogenolysis, maintains the blood glucose at its normal level; starvation has but little effect. Any interference with glycogen storage might become apparent by a fall of the glucose content of the blood after a short period of starvation. The patient went without food from 6 P. M. one evening until noon the next day, when the blood was taken

for examination. Analysis showed 0.064 per cent glucose, a fall of 0.009 per cent from the previous day. The result is at least strongly suggestive, though not alone to be taken as definite indication of any disturbance in glycogenolysis.

Fatty Infiltration.—A sort of antagonism between fat storage and carbohydrate storage has long been recognized (Rosenfeld(*a*)). When the power to store glycogen becomes impaired, fat is stored instead. In diabetes, for example, the capacity of the liver to store glycogen becomes impaired and fat is stored instead. In a starving dog, the amount of fat in the liver may rise to ten per cent. If carbohydrate, or protein which yields carbohydrate, be administered, the liver fat falls to about six per cent. If fat be given to a starving dog, the fat content of the liver may rise to 25 per cent; but if carbohydrate be ingested at the same time, the liver fat does not increase in this way (Rosenfeld(*b*)).

The same thing appears to take place in all forms of experimental impairment of the glycogen forming function. The normal fat content of the human liver is a little over three per cent (Heffter, von Stark). After phosphorus poisoning it may run up to 25 or 30 per cent or even more (Frank and Isaac(*b*), Heffter, von Höselin (von Stark). There is also an increase in the fat content of the muscles (Krehl(*a*) and Leick and Winkler). Wells(*c*) observed an increased fat content of the liver in cases of hydrazin poisoning. In one of his experiments on dogs, Porges(*c*) noted that during the operation of removing the adrenals the liver was normal; at necropsy, shortly afterward, it was observed that the liver had undergone fatty transformation. In other words, fat was stored instead of glycogen. In cases of hypopituitrism, another condition accompanied by hypoglycemia and muscular weakness, Cushing(*b*) has noted the occurrence of fatty transformation of the liver.

Exactly what happens in these cases is not entirely clear; but the delay in the disappearance of glucose from the blood after it has been administered (Frank and Isaac(*b*), Janney and Isaacson(*a*), Rosenthal(*b*), Underhill and Hogan) and the increase in the fat content of the blood at the same time (Underhill and Bauman(*b*)) strongly suggest that the glucose is transformed, not into glycogen, but into fat instead. And this hypothesis receives further support from the fact that the respiratory quotient rises at this time. The basal metabolism is also below the normal (Brock and Kay).

In view of the foregoing facts indicating a relationship between hypoglycemia, impaired glycogenesis, and fatty infiltration, the deposition of fat in the muscles in cases of muscular dystrophy which is responsible for the pseudomuscular hypertrophy can, with a strong probability of correctness, be attributed to an attempt on the part of the muscles to store fat instead of glycogen, a process quite in analogy with the process that takes

place in all other conditions in which there is a similar impairment of the carbohydrate metabolism.

In connection with the foregoing, it seems worth while suggesting that some cases of heart disease, especially the so-called "fatty degeneration" of the heart, may possibly be the result of an impairment, possibly local, of the carbohydrate metabolism, a condition that we might call pseudohypertrophic cardiodystrophy. This is certainly the case for the fatty degeneration of the heart occurring in severe diphtheria, and in certain endocrin diseases. These conditions lead to hypoglycemia and impaired glycogenesis; the organs, including the heart, store fat instead of glycogen. Only one blood analysis, in the case of a fatty heart, has been reported (McCrudden(*g*)), and that was very low, 0.0662 per cent. In this connection, the heart stimulating properties of adrenalin (a substance that increases the rate of glucose formation from glycogen) may be mentioned. Büdinger(*a*)(*b*) has recently suggested a similar hypothesis, namely, that certain cases of heart failure are the result of either an insufficient supply of glucose in the blood, or an inability to elaborate and store glycogen. He obtained very good results in such cases from injections of glucose solution. Pfalz, who followed out Büdinger's treatment in a number of cases, had very good results especially in cases of coronary sclerosis with angina pectoris.[4]

In this connection, it may not be out of place to suggest that just as the glucoside phlorizin has a profound local influence on the carbohydrate metabolism of the kidney, so may the actively stimulating digitalis glucosides have an effect on the carbohydrate metabolism of the heart.

Progressive Muscular Dystrophy as an Endocrin Disease

All forms of experimental interference with the glycogenesis-glycogenolysis mechanism appear to act either on the liver (and possibly on the muscles and other organs which store glycogen) directly, or on the endocrin glands which control the mechanism in the liver and other organs. Phosphorus poisoning and hydrazin poisoning, for example, cause direct liver damage. In cases of diphtheria toxemia, Addison's disease, and other conditions in which hypoglycemia follows damage or removal of the adrenals, thyroid, or hypophysis, the resulting effect on the glycogenesis-glycogenolysis mechanism is indirect; it is the consequence of an insufficient supply of the internal secretions which control the process.

It is possible to determine which of the two, liver or endocrin organs, is at fault, by the effect of epinephrin administration. Normally, or

[4] As this book goes to press I find two cases of progressive muscular dystrophy with post-mortem findings reported by Goodhart and Globus in which changes in the heart muscle were found similar to those found in the skeletal muscles.

when the liver is undamaged, administration of epinephrin (or other endocrin principle) decreases the glycogen of the liver (Agadschanianz; Doyon and Kareff(*a*), Gatin-Gruzewska), and thereby increases the glucose of the blood (Blum(*a*)(*b*), Zuelzer(*c*) and many others since then). But when the liver is damaged, as in the case of phosphorus poisoning or hydrazin poisoning, adrenalin does not increase blood sugar, at any rate, not to the same extent (Falta and Priestley, Frank and Isaac (*a*), Herter and Richards, Michaud, Pollack(*d*), Ringer(*a*), Velicke). During the first twenty-four hours after phosphorus poisoning, while the liver is still intact, epinephrin increases the blood sugar; after the first twenty-four hours the glycogenesis-glycogenolysis mechanism of the liver is so badly damaged that glucose can no longer be derived from it under the influence of epinephrin (Frank and Isaac(*b*)).

In the case of progressive muscular dystrophy, the prompt and marked rise in the blood sugar, and improvement in strength following administration of epinephrin and pituitrin indicates that the glycogenesis-glycogenolysis mechanism of the liver is not directly damaged. The hypoglycemia, the impairment in the power to store glycogen, the fatty infiltration, the creatinuria and the profound myasthenia, all symptoms which are characteristic of endocrin disease, strongly suggest that progressive muscular dystrophy is an endocrin disease. The delayed blood sugar curve (the delay in disappearance of sugar from the blood after glucose administration) is precisely similar to the delayed blood sugar curve in thyroidectomized dogs (Janney and Isaacson(*b*)).

Clinical evidence, suggesting an endocrin origin for muscular dystrophy, is seen in the trophic changes in the bones, tendons, and nails, in the dryness and abnormal pigmentation of the skin, hypertrichosis, and brittleness of the hair; in the distribution of the subcutaneous fat; and in the frequent occurrence of the disease in association with dwarfism, exophthalmic goiter, acromegaly, and underdevelopment of the genitalia (Janney, Goodhart and Isaacson).

It is probable that progressive muscular dystrophy is not a definite disease of one of the ductless glands, but rather a symptom complex that may result from disfunction of any one of several glands. A number of cases of muscular dystrophy have been reported in patients with hyperthyroidism (Boveri, von Werdt). Several cases with bony changes similar to acromegaly have been reported, pointing to pituitary involvement (Bregman, Eulenberg; Janney, Goodhart and Isaacson). The case reported by McCrudden and Sargent(*a*), showing such marked improvement under adrenalin and pituitary therapy, seems to have been one in which either the adrenals or the pituitary gland were involved. Several cases have been reported in which there appears to have been pineal involvement (Janney, Goodhart and Isaacson, Timme).

It is alleged that epinephrin decreases, and the internal secretion

of the pancreas increases the rate of sugar oxidation; and that normally the two tendencies—inhibiting and stimulating—just balance (Eppinger, Falta and Rudinger). Hyperglycemia is attributed to diminished glucose destruction resulting from a relative preponderance of adrenal activity. In accordance with this hypothesis, progressive muscular dystrophy might be attributed to a relative preponderance of pancreatic activity. But epinephrin does not decrease the rate of glucose oxidation, on the contrary, it increases it (Lusk(*c*)); and all evidence points to diminished glucose formation and not augmented glucose destruction as the cause of the hyperglycemia in progressive muscular dystrophy.

Progressive Muscular Atrophy

Progressive muscular atrophy is a disease of the central nervous system; the metabolism changes are secondary. The presence of creatin in the urine in this disease has long been known. In two cases reported by McCrudden and Sargent(*b*), the average daily quantities were 0.198 gram and 0.130 gram respectively. The blood sugar is normal, 0.111, 0.129, and 0.179 per cent respectively, in three cases reported by McCrudden and Sargent(*b*). The blood cholesterin is likewise normal.

As in other cases, the creatinuria indicates impaired glucose oxidation. In this case it is secondary, due to the fact that the muscles cannot function; glucose, though present in sufficient quantities, cannot be utilized.

Myasthenia Gravis

The metabolism data for myasthenia gravis are scanty. In two cases reported by McCrudden and Sargent(*b*), the blood sugar was 0.0818 and 0.095 respectively. These amounts average at about the very lowest limits for normal reported by the same authors. Creatin is not found in the urine (McCrudden and Sargent(*b*) and Gibson, Martin, and Buell). A low creatinin coefficient and a negative calcium balance have been found in this disease (Diller and Rosenbloom; Pemberton(*a*); Gibson, Martin, and Buell).

Amyotonia Congenita

Practically the only metabolic abnormality observed in this disease is a decrease in the creatinin excretion (Gittings and Pemberton, Pemberton(*b*); Powis and Raper, Spriggs; Ziegler and Pearce). The low creatinin is probably secondary to the atrophic condition of the muscles.

Metabolism in the Diseases of the Bones and Joints

. . . . . *Francis H. McCrudden*

Introduction—Diseases of the Bones—Normal Bone Metabolism—The Composition of the Bone in Disease—Metabolism Experiments in Osteomalacia—The Results of Histological Examination—The Cause of Abnormal Bone Metabolism—Acid Action in Osteomalacia—The Relation of the Ovaries to Osteomalacia—Need of Calcium as a Cause of Puerperal Osteomalacia—Summary: Puerperal Osteomalacia—Etiology of Other Disturbances of Bone Metabolism—Overproduction and Bone Disease—Diseases of the Joints.

Metabolism in Diseases of the Bones and Joints

FRANCIS H. Mc CRUDDEN

BOSTON

Introduction

Diseases of the bones and diseases of the joints cannot be sharply separated into two distinct groups. There are all gradations, from osteomalacia and osteitis deformans, which are, clinically, bone diseases, but with secondary changes in the joints, through rickets which is, clinically, a disease of the bones and joints, to atrophic arthritis, hypertrophic arthritis; and the trophic arthropathies such as Charcot's joints which are, clinically, joint diseases with secondary changes in the bones. And this is especially true when we consider the metabolism of these diseases, since the metabolic disturbances accompanying the bone changes, minor and secondary, from the clinical point of view, may overshadow the minor metabolic disturbances accompanying the joint changes.

For the present it will be best to accept the usual clinical classification and discuss only osteomalacia, rickets, osteoporosis, osteitis deformans, osteopsathyrosis, and osteogenesis imperfecta under bone diseases. Under diseases of the joints will be discussed the diseases usually clinically considered as arthropathies, even though the bone changes are the predominating feature from the standpoint of metabolism.

I. Diseases of the Bones

Point of view is of prime importance in discussing bone diseases. Rickets, for example, can be considered from the standpoint of the pediatrician, in which case its relation to other children's diseases and to the age of the patient will be emphasized. Osteomalacia can be considered from the standpoint of the obstetrician and gynecologist, in which case its relation to pregnancy, lactation and the ovarian activities will be emphasized. Treated from these points of view, very little emphasis will be placed on the most significant relationship of all, namely, the relationship

of these diseases to each other. This relationship is best brought out when these diseases are considered as disturbances of the calcium metabolism. From this point of view, these conditions are not distinct and separate in the sense that the specific infectious diseases are distinct and separate diseases, but they are very greatly exaggerated forms of conditions which are not uncommon, and scarcely to be considered pathological when present to but a slight degree. A person either has or has not typhoid fever, for example; there are no intermediary stages. Osteomalacia and rickets are more like obesity; there are all grades between the normal and extreme cases of the disease.

Bone, like other tissue, undergoes metabolism. Old bone is continuously absorbed and new bone is continuously replacing the old. In the case of growing children, as the skeleton hardens, the new bone laid down is progressively richer in calcium. In addition to acting as the supporting skeleton of the body, the bones act also as a storehouse of calcium salts, and consequently, if for any reason calcium salts are not furnished in sufficient quantities in the diet to satisfy the body requirements, or are needed elsewhere in the body in large amounts, the new bone laid down may be abnormally poor in calcium. As a result the bone becomes softer than it should be. If the deficiency in calcium is great enough to result in much bone softening, fragility and bending of the bone occurs, and the condition is diagnosed as osteomalacia, rickets, or osteoporosis.

This point of view has not always been held, however. Until recently bone was considered practically dead tissue, not undergoing metabolism once it was laid down; the decalcification of bone in osteomalacia was believed to be due to the action of an acid, an action similar to that which takes place when dead bone is put into acid.

From the time that osteomalacia was first recognized in the middle of the eighteenth century, its relationship to rickets has been under discussion. At first the two conditions were considered one disease by some authors, but clinical and anatomical differences which settled that question were soon discovered (Virchow(*c*)). Whether or not the process going on in the two conditions is essentially the same is another question. Early in the nineteenth century, microscopic and chemical examination of bone in osteomalacia showed decalcification similar to that which takes place when dead bone is placed in dilute hydrochloric acid. This appearance suggested that the condition is due to the action of an acid, which dissolves the mineral constituents and leaves behind the soft osteoid tissue, a point of view accepted by Virchow, Lobstein, and, in fact, most pathologists since. These investigators consider the processes in osteomalacia and in rickets entirely different, in that in osteomalacia the lime-free bone is believed to be normal bone from which the inorganic constituents have been dissolved out by an acid, whereas in rickets the lime-free bone is

believed to be newly made bone free from inorganic material. Cohnheim(*b*) was the first to express doubt concerning the correctness of this conception of the process. According to Cohnheim, the bones, even in the adult, are undergoing active anabolism and catabolism. In osteomalacia, when bone is destroyed, organic substances as well as lime salts are taken up by the osteoclasts, and then, just as in rickets, new bone made up of the organic matrix, but free from or poor in lime salts, is laid down. Evidence supporting either of these two opinions was not available at the time Cohnheim wrote.

Normal Bone Metabolism.—The conception that the mineral constituents of the body are dead, are not a part of the living body, and are not undergoing metabolism is a remnant of the old idea that there is a sharp distinction between the living or organic elements or compounds and the inorganic, an idea rejected long ago. During the past two decades many investigations, especially those of Loeb, have demonstrated incontestably that calcium and certain other inorganic elements are as much a part of "living" tissue as nitrogen, hydrogen, and oxygen. We do not have any difficulty in understanding that the small amounts of calcium, magnesium, and iron in the blood or muscles are used up—that is, catabolized and excreted—and have to be renewed, in other words, undergo metabolism; and it is difficult to understand why the pathologists who took Virchow's view could find difficulty in believing that the mineral salts of the bone undergo metabolism. If the muscle cells with their fraction of one per cent of mineral salts undergo metabolism, then why not also the bone cells with their fifty or sixty per cent mineral salts? We have no difficulty in understanding that the material of the blood plasma, or the connective tissue, or neuroglia fibrils must be renewed (Haidenhain). Why should there be any difficulty in understanding that the quite analogous bone should be renewed? *A priori* then, we should say that bone normally undergoes metabolism.

But there is more direct evidence of both bone anabolism and bone catabolism.

We have structural evidence of bone metabolism in the interlacing osseous plates of cancelli, which, depending on the direction of strain, are sometimes laid down in vertical columns, sometimes in oblique abutments. When as the result of accident or growth the strains and stresses change, the old material is absorbed and new material laid down, evidence of the metabolism being seen in the shifting of the lines of the cancelli to conform to the new pressure requirements (Schwatt). These alterations in minute structure, continuously adapting structure to function, are reflex changes under control of the nervous system. In response to centripetal impulses, set up by the pressure stimuli in the joints and bones, and passing to the central nervous system, centrifugal impulses controlling the bone metabolism pass back. If the nervous mechanism breaks down, the

bone laid down may become chemically and physically abnormal. Thus, in tabetic patients, when the arc for deep reflexes from the knees becomes broken, one of the results may be a Charcot joint, one feature of which is an osteoporosis, with a complete loss of the normal architectural features of the adjacent bones. In cerebral palsies, poliomyelitis, tabes, and syringomyelia, we often see rarefaction and atrophy of bone (Hunt, Stewart). In various myopathies, the long bones of the limbs corresponding to the affected muscles undergo rarefaction and atrophy, and the normal ridges for muscular attachments become smoothed down (Merle and Raulot-Lapointe). We have evidence of bone metabolism also in the disuse atrophy and rarefaction, so frequently observed in roentgenograms of patients, with a limb immobilized in plaster, and in patients with wasting diseases, and in the bone softening seen in the enfeebling diseases—influenza, visceroptosis (Barker(*a*)). Acute bone atrophy demonstrable in X-ray plate is very common.

A generation ago, Pommer(*a*) pointed to the presence of osteoblasts in bone at all ages as evidence of continuous bone metabolism, and Tomes and Morgan offered such evidence more than two generations ago.

We have evidence of active bone anabolism in the formation and subsequent calcification of the callus following a fracture.

Active bone catabolism is seen during starvation. Thus, it was shown that the professional fasters, Cetti and Breithaupt, after a week to ten days of starvation, were excreting nearly as much calcium per day as in the beginning (Lehman, Muller, Munk, Senator and Zuntz(*b*)). The amount of flesh catabolized could be calculated from the amount of nitrogen excreted; and, the amount of calcium in flesh being known, it could be shown that the amount lost was more than could be accounted for, unless it was assumed that it came from the bones. Similar calculations from figures obtained by Benedict(*d*), on a man who starved thirty-one days, show that 93 per cent of the calcium excreted must have come from the bones. Munk's(*a*) and Muller's studies of starving dogs show the same thing. Forster(*b*) fed a dog a diet poor in calcium for twenty-six days. In that time the dog lost 13.57 grams calcium over and above that taken in the food. Analysis of the different organs demonstrated that this must have come chiefly from the bones.

Besides such metabolism experiments we have direct analysis of the bones showing that the mineral constituents are used up during starvation. Voit's experiments(*a*), which were the first to show that the bones lose weight during starvation, cannot be used as evidence because he did not show that the mineral constituents decrease. Weiske's(*d*) negative results, in the case of starving dogs, are likewise inconclusive, on account of the short duration of the experiments (seven to eleven days). Sedlmair

(*b*), whose experiments are both interesting and conclusive, starved cats for a month or more, analyzed the excreta, and, at the end of the period, analyzed the bones and compared the results with those of normal cats. The amount of calcium excreted which came from the bones was equivalent to one per cent per day of the total bone of the cat. Sedlmair's bone analyses showed in addition that there was a loss of from 4.6 to 13.8 per cent of the ash, and from 2.5 to 11.6 per cent of the calcium oxid of the bones. In one cat there was a loss of 13.8 per cent ash, 11.6 per cent calcium oxid, and 12.8 per cent ossein—results which are close enough to suggest that the organic and inorganic materials of the cell are destroyed together. Wellman has found similar results in the rabbit.

Studies of the phosphate metabolism lead to the same conclusion as studies of the calcium metabolism. It is commonly stated that the excretion of nitrogen and phosphorus are nearly parallel; that the ratio N:P in the excreta is almost constant, and, on the average, is about the ratio in which these elements occur in flesh, so that theoretically the phosphorus excretion might be roughly used as a measure of protein metabolism. The belief is probably based on the statements of Zuelzer, although his own tables do not show such constancy, but, on the contrary, show great variation in the ratio. More recent experiments (Buchmann) show that the phosphorus and nitrogen excretion vary quite independently, even on a constant diet (Kellar); and the amount of phosphorus metabolized may be much greater than could come from the flesh metabolized. Determination of the ratio of nitrogen to phosphorus in different tissues have been made (Lehman, Muller, Munk, Senator and Zuntz(*b*), Cronheim and Muller), so that, from the amount of nitrogen excreted in starvation, we can calculate the corresponding amount of phosphorus. This has been done (Lehman, Muller, Munk, Senator and Zuntz(*b*), Renvall(*a*)), and there was always a greater excess of phosphorus that must have come chiefly from the bones, since it has been shown that the dry brain and cord, the other phosphorus-rich tissues, do not lose weight in starvation (Voit (*a*)). Calculation from the data of older results, for example, those of Forster(*a*), show the same result.

The Composition of the Bone in Disease.—Chemical analyses long ago showed that the amount of mineral matter, and especially the amount of lime salts, in the bone in osteomalacia is decreased. The earliest analysis, a rough one of Bostock, showed but twenty per cent of earthy matter in the bone in a case of this disease. But in this case, and also in the analyses of Marchand, Bogner, Ragsky and von Bibra, the authors did not report their results in such form that they can be compared with later results. That the proportion of inorganic matter is decreased, and that of organic matter increased is shown by Tables 1 and 2, giving the percentage of each in the bone.

TABLE 1

COMPOSITION OF NORMAL BONE

	Inorganic Matter Percentage	Organic Matter Percentage
Frerichs	65.9—70.2	29.8—34.1
Lehmann	69.2	32.28
Zalesky	65.44	34.56
Langendorff and Mommsen	54.24	45.76

TABLE 2

COMPOSITION OF BONE IN OSTEOMALACIA

	Inorganic Matter Percentage	Organic Matter Percentage
Durham	45.37	54.63
Huppert	25.71	74.29
Moers and Muck	38.23	61.77
Moers and Muck	35.11	64.89
Langendorff and Mommsen	37.8	62.2
Cappezuoli	42.66	57.54
Cappezuoli	50.91	49.09
Badolle	43.05	56.95
Badolle	43.5	56.5
McCrudden (human bone)	48.54	28.02
McCrudden (horse bone)	35.61	64.39

The calcium in the dried bone may be decreased to nearly one-half its normal value (Table 3).

TABLE 3

PERCENTAGE OF CALCIUM OXID IN DRIED BONE

	Normal	Osteomalacia
Moers and Muck	.....	17.36
Moers and Muck	.....	18.07
Cappezuoli	.....	14.83
Cappezuoli	.....	13.11
Badolle	.....	10.5
Badolle	.....	21.4
McCrudden (human)	28.85	15.44
McCrudden (horse)	33.30	19.22

Not only the calcium of the bone as a whole, but also the amount of calcium in the ash is decreased (Table 4). In other words, the relative amount of the other mineral constituents of the ash is increased.

The amount of P_2O_5 in the dried bone is decreased (Table 5). On comparing Table 3 with Table 5, it will be seen the decrease in phosphate is only to about two-thirds the normal, whereas the decrease in calcium in the same cases is to nearly one-half the normal. In other words, the ratio P_2O_5 : CaO in the bones in osteomalacia is greater than the normal ratio.

TABLE 4

PERCENTAGE OF CALCIUM OXID IN BONE ASH

	Normal	Osteomalacia
Zalesky	52.64—53.06	.....
Langendorff and Mommsen	53.05	44.48
Gabriel	53.31	.....
Huppert	.....	45.41
Moers and Muck	.....	50.66
Moers and Muck	.....	45.47
Cappezuoli	.....	36.05
Cappezuoli	.....	32.75

TABLE 5

PERCENTAGE OF PHOSPHATE (P_2O_5) IN DRIED BONE

	Normal	Osteomalacia
Moers and Muck	.....	18.20
Moers and Muck	.....	14.38
Cappezuoli	.....	12.81
Cappezuoli	.....	11.66
Badolle	.....	7.8
Badolle	.....	14.1
Badolle	.....	14.0
McCrudden (human)	19.55	12.01
McCrudden (horse)	23.44	16.28

The phosphate content of the ash is rather variable. On comparing Tables 5 and 6, it will be seen that although the amount of phosphate in the dried bone is decreased to about two-thirds the normal, the amount in the ash is nearly unchanged. In other words, the decrease in the amount of calcium in the ash is partly made up by an increase in the relative amount of phosphate.

TABLE 6

PERCENTAGE OF PHOSPHATE (P_2O_5) IN BONE ASH

	Normal	Osteomalacia
Zalesky	38.49—39.02	.....
Langendorff and Mommsen	43.93	34.76
Gabriel	36.65	.....
Huppert	.....	39.26
Moers and Muck	.....	47.67
Moers and Muck	.....	43.00
Cappezuoli	.....	31.12
Cappezuoli	.....	29.15

The amount of magnesium is increased. This, taken in connection with the changes in calcium and phosphate content, means that the ratio of the magnesium phosphate to that of the calcium phosphate is increased over the normal. This alone is sufficient evidence to reject the hypothesis

that the process in osteomalacia is one of simple halisteresis comparable with the action of an acid on dead bone. It is impossible to imagine how an acid can dissolve the calcium phosphate and leave the more soluble magnesium phosphate undissolved. Furthermore, if we could imagine such a condition, then, when the calcium was decreased in amount to one-half the normal, the relative amount of magnesium would be only doubled. But our tables show an increase in the magnesium of more than four-fold, which means that there is an increased deposition of magnesium. Some investigators analyzed the dried bone (Table 7), and others analyzed the ash; of the latter, some report their results in terms of magnesium oxid (Table 8), and others in terms of magnesium phosphate (Table 9). Tables 10 and 11 bring out especially well the enormous increase in the magnesium content of the bone; in Table 10 the average relative increase is nine-fold, in Table 11 thirty-fold.

TABLE 7

PERCENTAGE OF MAGNESIUM OXID IN DRIED BONE

	Normal	Osteomalacia
Moers and Muck	.....	0.484
Moers and Muck	.....	0.902
Cappezuoli	.....	0.60
Cappezuoli	.....	0.46
McCrudden (human)	0.14	0.57
McCrudden (horse)	0.105	0.48
Badolle	.....	0.23
Badolle	.....	1.2

TABLE 8

PERCENTAGE OF MAGNESIUM OXID IN BONE ASH

	Normal	Osteomalacia
Zalesky	0.405—0.521	.....
Gabriel	0.77	.....
Huppert	....	4.46
Moers and Muck	....	1.267
Moers and Muck	....	2.528
Cappezuoli	....	1.12
Cappezuoli	....	1.49

TABLE 9

PERCENTAGE OF MAGNESIUM PHOSPHATE IN BONE ASH

	Normal	Osteomalacia
Gorup-Besanez	1.04	....
Gegenbauer	1.75	....
Huppert	....	9.6
Chabrié	....	26.9

TABLE 10

RATIO OF CA : MG IN DRIED BONE, NORMAL AND OSTEOMALACIA

Investigator	Ratio of Ca to Mg in the Bone	
	Normal	Osteomalacia
McCrudden	1 : 0.005	1 : 0.037
McCrudden	1 : 0.003	1 : 0.025
Moers and Muck	.....	1 : 0.028
Moers and Muck	.....	1 : 0.050
Badolle	.....	1 : 0.022
Badolle	.....	1 : 0.056
Cappezuoli	.....	1 : 0.027
Cappezuoli	.....	1 : 0.039
Average	1 : 0.004	1 : 0.036

TABLE 11

RATIO OF CA : MG IN BONE ASH (NORMAL AND OSTEOMALACIA)

Investigator	Ratio of Calcium to Magnesium	
	Normal	Osteomalacia
Zalesky	1 : 0.009	.....
Gabriel	1 : 0.015	.....
Huppert	.....	1 : 0.980
Moers and Muck	.....	1 : 0.028
Moers and Muck	.....	1 : 0.050
Cappezuoli	.....	1 : 0.027
Cappezuoli	.....	1 : 0.039
Badolle	.....	1 : 0.021
Badolle	.....	1 : 0.059
Average	1 : 0.012	1 : 0.172

It is interesting to note that the same great increase in magnesium was observed in a case of artificial osteomalacia, induced in a rabbit by the repeated injection of glucose (Badolle). With a fall of about twenty per cent in the calcium content of the bone, there was a five-fold increase in the magnesium (Table 12).

TABLE 12

DISPROPORTIONATE INCREASE OF MAGNESIUM IN BONE IN ARTIFICIAL OSTEOMALACIA

	Per Cent CaO In Bones	Per Cent MgO In Bones	CaO : MgO
Normal	31.66	0.60	1 : 0.019
Osteomalacia	24.8	3.04	1 : 0.123
Change in composition	−22.	+ 506.	

The increase in magnesium strongly suggests that this element is used in part to supply the deficiency in calcium. The quite opposite

physiological action of the magnesium and calcium ions does not come into consideration here. We merely have a partial substitution of magnesium phosphate for calcium phosphate as a structural material.

Such a substitution has been experimentally reproduced.

Koenig fed three sets of young rabbits food poor in calcium phosphate. Then to the diet of one set calcium phosphate was added; to the diet of a second set, magnesium phosphate; and to the diet of the third set, strontium phosphate. The rabbits which were given magnesium phosphate were found to have twice as great an absolute amount of magnesium in the bones as the others. In the case of the rabbits fed strontium phosphate, an element foreign to the body, the amount of calcium in the bones was decidedly decreased, and about five per cent strontium found instead. Table 13 shows the figures obtained in these experiments.

TABLE 13

EFFECT OF CALCIUM, MAGNESIUM, AND STRONTIUM CONTENT OF THE DIET ON BONE COMPOSITION

	Per Cent Ca In Bones	Per Cent Sr In Bones	Per Cent Mg In Bones
Calcium phosphate added to the diet..	a51.36	....	0.70
	b51.92	....	0.82
Strontium phosphate added to the diet	a44.77	5.21	0.64
	b49.27	4.71	....
	c46.78	5.37	1.09
Magnesium phosphate added to the diet	a51.60	....	1.48
	b51.92	....	1.68

The earlier experiments of Weiske(*b*), in which he used adult animals, gave negative results; but later experiments(*c*), in which he used young animals, gave results similar to those of Koenig.

Table 14 shows Weiske's figures.

TABLE 14

EFFECT OF CALCIUM, MAGNESIUM, AND STRONTIUM CONTENT OF THE DIET ON BONE COMPOSITION

	Per Cent CaO In Bones	Per Cent MgO In Bones	Per Cent SrO In Bones
Calcium carbonate added to the diet..	31.43	0.73	....
Magnesium carbonate added to the diet	28.36	1.39	....
Strontium carbonate added to the diet.	23.02	0.61	4.09
Nothing added to the diet.....	28.85	0.63	....

More recent studies of Weiser show this same replacement of calcium by magnesium on a diet poor in calcium, but containing an abundance of magnesium (Weiser(*a*)).

The results in the case of sulphur are of especial interest (Table 15).

TABLE 15

PERCENTAGE OF SULPHUR IN DRIED BONE

	Normal	Osteomalacia
McCrudden (human)	0.14	0.55
McCrudden (horse)	0.10	0.37

The organic matrix of bone is made up largely of glycoproteins which, compared with most other proteins, are rich in sulphur; so that in osteomalacia, a condition in which the percentage of organic matter is increased, we should expect to find an increased amount of sulphur. But if the process were a halisteresis, similar to that which takes place when bone is subjected to the action of acid, we should expect, in cases like the two cited by McCrudden, in which the calcium has decreased to nearly half its normal value, to find the amount of sulphur, correspondingly, only doubled, whereas in both cases it has increased nearly four-fold. This, again, as in the case of magnesium, suggests that there is an apposition of new tissue, in this case an apposition of tissue similar to the organic matrix of normal bone.

Less complete analyses are available for diseases other than osteomalacia. A two- to three-fold increase in the magnesium content of the bone has been found in osteitis deformans. Thus Tourette and Magdelaine found the ratio of magnesium to calcium in the bone in this disease 11:1000; and Robin found it 18:1000. The ratio in normal bone is 5:1000 (McCrudden(*d*)). In rickets Gassman found a twelve per cent fall in the percentage of calcium in the bones, accompanied by an increase of more than five hundred per cent in the magnesium content. Cattaneo found a similar decrease in calcium and increase in magnesium. (Table 16.)

TABLE 16

CHANGE IN COMPOSITION OF BONES IN RICKETS

	Normal Ribs Mean of Two Cases	Rachitic Ribs Mean of Two Cases	Percentage Change
Percentage of Ca	24.40	21.48	— 12.
Percentage of Mg	0.10	0.64	+ 540.
Ratio of Ca to Mg	1 : 0.004	1 : 0.030	

To *summarize* the results of bone analyses: In osteomalacia the proportion of inorganic constituents is decreased and the proportion of organic constituents increased. The decrease in inorganic constituents is due to a loss of calcium phosphate. The proportion of magnesium phosphate and of the organic matrix of the bone is increased. The increase is

greater than can be accounted for by simple halisteresis; we must assume that it is due to material newly laid down to replace the calcium phosphate.

Metabolism Experiments in Osteomalacia.—If, as the bone analyses seem to indicate, the apposition of calcium is decreased, and the apposition of magnesium and sulphur-rich osseoid tissue increased, we might expect examination of the results of metabolism experiments in the active period of the disease to show a disturbance of the equilibrium in the case of these elements. Moers and Muck, Schmuzinger, Fehling(*b*), Denecke, and Schuchardt made quantitative determinations of the calcium in the urine in osteomalacia, but, since calcium is excreted chiefly in the feces, and these investigators examined neither food nor feces, their results are of little value. Table 17 gives a summary of all the metabolism observations, with certain exceptions, reported in the literature. The exceptions were those carried out on a patient who was recovering, the case of one patient who was far advanced in pregnancy, and the case of one patient who had suffered many years, and was so severely afflicted that treatment did not afford even temporary relief. These exceptions will be discussed later when the importance of the effect of stage of the disease on the metabolism, an important and generally overlooked point, is taken up.

TABLE 17

CALCIUM METABOLISM IN OSTEOMALACIA

Investigator	Duration of Observation in Days	Grams CaO in the Food	Grams CaO in the Excreta	Grams CaO Lost by Body
Limbeck	5	2.965	5.604	2.642
Korczynski	4	.....	.....	loss of CaO
His	11	8.66	9.48	0.82
His	7	6.08	7.24	1.16
Neumann	5	11.26	11.65	0.39
Hotz	8	10.78	12.73	1.95
Goldthwait, Painter, Osgood, and McCrudden	8	4.56	5.66	1.10
McCrudden	6	3.44	8.27	4.83
McCrudden and Fales	10	21.17	22.14	0.97
Freund and Lockwood	7	7.75	8.22	0.47

It will be seen from Table 17 that there is always a loss of calcium by the body, a result in accord with the low calcium content of the osteomalacia bones. The significance of this loss of calcium is made more striking in the studies carried out by McCrudden, at any rate, by the fact that there was a positive balance of sulphur, nitrogen, magnesium, and phosphorus at the same time.

Studies of the phosphorus metabolism have given variable results. Later, after we have considered the calcium metabolism in different stages of the disease, the reason for the variable results will be clear.

Corresponding with the increased magnesium content of osteomalacia bone, we find that the body is retaining magnesium (Table 18).

TABLE 18

MAGNESIUM METABOLISM IN OSTEOMALACIA

Investigator	Duration of Observation in Days	Grams MgO in Food	Grams MgO in Excreta	Grams MgO Retained by Body
Goldthwait, Painter, Osgood, and McCrudden	8	2.207	2.015	0.192
McCrudden and Fales	10	4.69	4.55	0.14

In the case of sulphur, again, as in the case of magnesium, we find a retention corresponding to the increased amount of the element found in the bone (Table 19).

TABLE 19

SULPHUR METABOLISM IN OSTEOMALACIA

Investigator	Duration of Observation in Days	Grams S in Food	Grams S in Excreta	Grams S Retained by Body
Goldthwait, Painter, Osgood, and McCrudden	8	7.15	2.68	4.47
McCrudden and Fales	10	10.03	8.14	1.89

The question arises: Are the amounts of elements gained and lost in these studies outside the limits to be expected in a normal case? Are the figures significant?

Consider, for example, the ten-day experiment of McCrudden and Fales(*b*) (Table 20), the case in which the daily loss of calcium was least.

TABLE 20

TEN DAY METABOLISM OBSERVATION IN OSTEOMALACIA

	N Grams	CaO Grams	MgO Grams	S Grams	P_2O_5 Grams
Urine total	99.68	3.344	1.151	7.112	19.11
Feces total	11.72	18.80	3.40	1.024	15.57
Total outgo	111.4	22.14	4.55	8.14	34.68
Total intake (in food)	121.4	21.17	4.69	10.03	35.55
Retention	10.0	.....	0.14	1.89	0.87
Loss	.....	0.97	.....	.....	.....
Percentage retained	8.3	.....	3.0	18.8	2.4
Percentage lost	.....	4.6	.....	.....	.....

The amount of CaO lost in ten days was about 1.0 gram. But this is nearly five per cent of the amount in the food, and over three times the average daily amount in the urine; and the loss is probably chiefly through the urine, since the amount in the urine is nearly double the normal. Furthermore, everything else was being retained, the retention running from three per cent in the case of magnesium to nineteen per cent in the case of sulphur. At the time of the investigation, the patient was in relatively good condition. If we could have studied her condition when the process was more active, even greater losses, such as were found in some of the other studies, would probably have been found. In one of the experiments of McCrudden, there was an average daily loss of nearly one gram of CaO per day. And Berger(*b*) speaks of a case in which he found in the urine 9.0 grams CaO per day. All these variations are far outside normal limits. Towle has pointed out that, unless very large quantities of calcium are administered, there is a close parallelism between calcium and nitrogen metabolism in health. The same holds true for the other elements. And when there is retention, as for example during pregnancy, there is a parallelism between the amount of nitrogen and mineral salts retained (Hoffström). Table 21 shows how close the parallelism may be in a normal person (McCrudden and Fales(*b*)).

TABLE 21

INTAKE AND OUTGO OF HEALTHY BOY

	N Grams	S Grams	CaO Grams	MgO Grams
Total intake	86.10	6.138	14.99	3.26
Total outgo	71.46	5.222	12.42	2.53
Balance	14.64	0.916	2.57	0.73
Per cent retention	+ 17.0	+ 14.9	+ 17.1	+ 22.4

The data from metabolism observations in different stages of osteomalacia demonstrate the significance of the figures in another way. They bring out the close correspondence between the clinical condition of the bones and the metabolism of the constituents of the bones (Tables 22, 23, 24).

TABLE 22

INTAKE AND OUTGO DURING ACTIVE STAGE OF OSTEOMALACIA

8 Days	Grams CaO	Grams MgO	Grams P_2O_5	Grams S	Grams N
Total intake	4.56	2.207	12.05	7.15	69.12
Total excreted	5.66	2.015	12.37	2.68	63.02
Retention	....	0.192	.....	4.47	6.10
Loss	1.10	.....	0.32	....	.....

TABLE 23

INTAKE AND OUTGO IN OSTEOMALACIA DURING A PERIOD OF IMPROVEMENT (AFTER OVARIOTOMY)

14 Days	Grams CaO	Grams S	Grams N
Total excreted	7.20	4.84	104.3
In food	10.03	10.54	127.0
Retained	2.83	5.70	22.7

TABLE 24

INTAKE AND OUTGO IN OSTEOMALACIA AFTER RELAPSE

6 Days	Grams CaO	Grams MgO	Grams P_2O_5	Grams S	Grams N
Total excretion	8.27	1.764	10.35	2.793	34.68
In food	3.44	1.504	12.28	2.897	38.85
Retained	....	.....	1.93	0.104	4.17
Lost	4.83	0.260			

The study shown in Table 22, with a loss of calcium and a retention of sulphur and magnesium, was carried out during the active stage of the disease (Goldthwait, Painter, Osgood and McCrudden).

The study shown in Table 23 was carried out after removal of the ovaries, and at a time when the patient showed such marked clinical improvement that union of an ununited bone, the result of an osteotomy, took place. The clinical improvement was accompanied by a retention of calcium. Sulphur was still retained, but not in such excess as during the active period of the disease. Thus Table 22 (active period) shows the ratio of sulphur retention to that of nitrogen as 73:100; as clinical improvement began, the ratio fell to 25:100 (Table 23).

The study shown in Table 24 was carried out more than a year later. Just before this study was made, the condition began to grow worse; two spontaneous fractures had occurred a few weeks previously. Corresponding with the clinical relapse there was a marked negative calcium balance. The intake and outgo of sulphur nearly balanced at this time.

The studies shown in Tables 23 and 24 were made soon after the change in direction of the calcium metabolism had begun, if we may judge this by the onset of change in the clinical condition for better or worse. It will be noticed that in both cases there is a delay in the corresponding inverse change in direction of sulphur and magnesium balance. The significance of this lag will be discussed later.

There are a few other metabolism observations in the literature, made during recovery from osteomalacia.

Neumann(*a*) cites the case of a woman with osteomalacia who gave birth to a child on January ninth, began to show improvement about March first, and was, apparently, clinically well by April first. A com-

plete metabolism study of seven days made during the period of improvement (March twenty-ninth to April fourth), showed a calcium retention of 3.8 grams (intake 29.2 grams, outgo 25.4 grams).

In another case studied by Neumann(*b*), clinical improvement followed castration. During the active stage of the disease, the patient showed a negative calcium balance (Table 17). After improvement began, a five-day study showed: intake of CaO 12.98 grams, outgo 7.20 grams; retention 5.78 grams.

His(*d*) and Hotz have studied the calcium balance in cases of osteomalacia during the active period, during a period of improvement following phosphorus administration, and afterwards following relapse, with the same results (Table 25).

TABLE 25

COMPARISON OF CALCIUM BALANCE IN THREE STAGES OF OSTEOMALACIA: A, DURING THE ACTIVE STAGE; B, DURING IMPROVEMENT; AND C, DURING A RELAPSE

		His		Hotz	
			Grams		Grams
Active period	intake	11 days	8.66	8 days	10.78
	outgo		9.48		12.73
	balance		— 0.82		— 1.95
Improvement	intake	9 days	6.47	12 days	17.67
	outgo		4.06		17.32
	balance		+ 2.41		+ 0.35
Relapse	intake	7 days	6.08	15 days	20.24
	outgo		7.24		21.50
	balance		— 1.16		— 1.26

Less complete metabolism data are available for the other bone diseases, but the data are in harmony with our view regarding the nature of the process in osteomalacia. Thus Bookman(*a*) found a negative calcium balance with a positive balance for phosphorus, sulphur, and nitrogen in a case of osteopsathyrosis. And the same author(*b*) found the retention of calcium decidedly below the normal in the case of a child with osteogenesis imperfecta.

Metabolism experiments in rickets, during the active period of the disease, show either a negative calcium balance or only a very slight positive balance, one that is far below normal. Just before the onset of clinical improvement, the calcium balance becomes positive; the amount retained increases until, during convalescence, the retention may become two or three times the normal. Later, after recovery, the retention falls to normal again (Schabad(*b*)).

To *summarize* the results of metabolism experiments: We find that the body is losing calcium and retaining magnesium and sulphur. These results are in accord with those obtained by bone analyses, and confirm the supposition that in osteomalacia the process is not one of simple passive halisteresis, but an active one of increased bone metabolism. Old bone is destroyed and new bone laid down. But the new bone is similar to the organic matrix of bone, and is free from, or poor in, calcium phosphate, instead of which there is a partial replacement of the calcium phosphate by magnesium phosphate.

The Results of Histological Examination.—The next question to be answered is whether or not histological investigations offer anything in support of our chemical investigations.

If we examine rachitic bones, we find osteoid tissue, that is, the organic matrix of bone without the lime salts, at the junction of epiphyses and diaphyses, as well as beneath the periosteum. If we examine the bone in osteomalacia, we find similar osteoid tissue, not, as in rickets, beneath the periosteum and at the boundaries of epiphyses and diaphyses, but in the interior of the bone in proximity to the Haversian canals. Yet, in the former case, the osteoid tissue has been considered new lime-free bone, and, in the latter case, old decalcified bone. There has been no good reason for this belief except the unjustified assumption that, when once laid down, bone is dead tissue not undergoing metabolism.

Cohnheim(*b*) was the first to correctly describe normal bone metabolism and to express the opinion that the process in osteomalacia is not one of halisteresis, but is essentially the same as that in rickets. Cohnheim is worth quoting, no better statement of the process having yet been made:

(P. 630.) "In rachitic bones there is found at the junction of epiphysis and diaphysis, as well as immediately beneath the periosteum—in every situation, in short, where new bone should be formed, a more or less compact, soft material, which is sometimes gelatinous, varies in quantity with the intensity of the disease and is known as osteoid tissue. This substance is nothing more or less than the organic ground substance of bone, without the bone-earth which should be combined with it."

(P. 631.) "As to the histological appearance of the bones in true osteomalacia . . . they consist in the substitution of osteoid zones for the typical osseous tissue. These zones are not, however, situated beneath the periosteum and at the boundaries of the epiphyses, as in rickets, but occupy essentially the interior of the fully formed bone in immediate proximity to the Havesian canals."

(P. 632.) "Lastly, we have to determine the nature of the zones of osteoid tissue occupying the interior of the bones in osteomalacia proper. The most widely accepted view is that this tissue originates in an active decalcification, that fully developed normal bone had previously existed at the seat of the osteoid tissue, and has been deprived of its lime salts by a pathological process. Accordingly, the process is represented as strictly analogous to the method of decalcification adopted, with a view to microscopical examination of a bone."

After expressing his disbelief in this commonly accepted view, he goes on to say:

"Nature adopts a different method in effecting the absorption of bone. The salts are not first extracted and the ground substance afterwards absorbed. Wherever bone disappears, Howship's lacunæ are at once formed and filled with osteoclastic giant cells. The minutiæ of the process of bone resorption are indeed still completely unknown to us, but it is certain that at no stage does an osteoid tissue free from lime occur."

(P. 633.) "The osteogenic zones . . . must have originated solely by apposition. That the bones are for a long time—certainly till the age of vigorous manhood—the subjects of an uninterrupted and coincident apposition and resorption, from which even the interior of the compact ground substance is not exempt, is a thoroughly established fact. The distinctive criterion of oeteomalacia would accordingly be the apposition of ground-substance, free from earthy salts, i.e., of osteoid tissue, instead of normal osseous material. It appears then, that rickets and true osteomalacia are very closely allied diseases, since both depend on the apposition of an osteogenic substance free from lime in place of typical osseous tissue. We may, in fact, dispense with a discussion of the many points of dissimilarity, inasmuch as these may be inferred from the difference of the ages of the individuals affected, i.e., from the state of development of the skeleton."

Langendorff and Mommsen, who were studying osteomalacia at the time Cohnheim wrote, were struck by the great similarity of the bone in their case of osteomalacia to new osteoid tissue, and suggested that in their case, and, perhaps, in some other cases, Cohnheim's hypothesis might apply. But otherwise Cohnheim's hypothesis seems to have made little impression.

In 1891 Recklinghausen(*b*), in an exhaustive report on the histology of osteomalacia and similar conditions, called attention to the abundance of osteoblasts and Sharpey's fibers and to the "youthful appearance," as he calls it, of many of the bone corpuscles as evidence that the osteoid tissue is new tissue. He refers to the fact that patients with osteomalacia often start a good callus formation. In an elaborate account of a continuation of this work, published in two large volumes in 1910 (Recklinghausen(*c*)), and containing röntgenographs, as well as histological studies of all conditions at all similar to osteomalacia, von Recklinghausen completely confirms his earlier views and retracts certain doubts expressed in his earlier paper. He states definitely that rickets, osteoporosis, and osteomalacia cannot be differentiated morphologically.

Other investigators have confirmed the findings of von Recklinghausen (Looser(*a*), Axhausen, also Gayet and Bonnet). Meek has pointed out that certain spicules of bone in osteomalacia are in process of absorption, as shown by the presence of osteoclasts lying in the lacunæ at their edges; other spicules are surrounded by closely applied osteoblasts, and evidently consist of newly formed bone in which calcification has failed. And Tashiro has pointed out that there is abundant newly formed osteoid tissue which can be distinguished from the old decalcified tissue (of which there appears to be some) by being not in layers, but contiguous to, and continuous with young proliferating endosteum; this tissue contains an abundance of osteoblasts.

Hanau's finding of histological changes similar to those in osteomalacia, at postmortem examinations of the bones, especially the pelvic

bones, of many pregnant women showing no evidence of abnormal bone changes during life, is in accord with the conception that the osteoid tissue is newly laid down bone, and not old decalcified bone, for he, too, found osteophytes in this tissue. Several older writers mention the finding of a mild grade of osteomalacia in apparently healthy pregnant women, but their findings seem to have made no impression. The facts have been more recently confirmed by Wild.

Another bit of evidence to support the theory of bone metabolism outlined here, is afforded by Dibbelt's observation, that when recovery from osteomalacia, experimentally induced in pregnant dogs, takes place, the decalcified bone substance present in the active stage does not later become calcified; it is absorbed and replaced by *new* calcified bone.

The findings is osteitis deformans indicate that the abnormal bone is of the same or of a very similar character to that in osteomalacia. Von Recklinghausen(*b*) was the first to point out that osteitis deformans may be regarded as a local osteomalacia. On the basis of histological examination, Schmieden, Tashiro, and Higbee and Ellis, have independently come to the same conclusion.

Histological examination, structural evidence, alone could not be conclusive regarding the physiological nature of the process. Whether Virchow or Cohnheim was correct could only be a matter of conjecture until the physiological chemical evidence became available. The histological evidence is, however, in accord with the chemical evidence in indicating that the process in osteomalacia consists in a replacement of the normal bone by new calcium-free bone, or bone poor in calcium.

Summary.—To sum up our conclusions concerning the process in osteomalacia, osteoporosis, osteitis deformans, rickets, and similar conditions: The skeleton is made up of live tissue undergoing metabolism. The bones are the seat of an uninterrupted and coincident process of apposition and absorption throughout life. During infancy and childhood, as the uncalcified bone is gradually absorbed, the new bone laid down to replace it becomes progressively richer in lime salts; the rate of apposition of lime salts to the bone is more rapid than absorption from the bone. If this is not the case, and the new bone which should contain lime salts is free from lime, the soft osteoid bone bends under the weight of the body, the child becomes rickety. Bone metabolism is going on too in later life, and if the anabolism of lime-containing bone does not keep pace with its catabolism, the bones become poorer in lime salts; when this condition is extreme, the bones become soft. In old age, when anabolic processes are retarded, a condition of increased metabolism of bone may not be followed by increased apposition of even lime-free osteoid tissue, and the result may be the condition of osteoporosis, known as senile osteomalacia. The abnormal condition may be circumscribed, affecting

only a small portion of the bone, in which case the result is osteitis deformans.

This point of view renders adolescent rickets more intelligible, and serves to clear up the controversy regarding so-called infantile osteomalacia. Rehn(*a*)(*b*), His(*d*), Siegert, and von Recklinghausen(*b*) have reported certain cases which they differentiated from rickets and called infantile osteomalacia, a diagnosis disputed by Ziegler, who called the condition rickets. From the old point of view, implying an essential difference in the nature of the process in the two diseases, the controversy had some significance. From our point of view it is not significant; the difference between rickets and infantile osteomalacia is probably largely one of severity. In a severe enough case of rickets, the body may fail to supply sufficient lime salts, not only to uncalcified bones and parts of bones which are due to become calcified, but may also destroy bone which has already become calcified, and lay down new osteoid tissue instead.

The Cause of Abnormal Bone Metabolism.—The causes which have been conjectured as responsible for the abnormal bone metabolism in osteomalacia, rickets and similar conditions, may be divided into exogenous agencies of a general nature, such as bad hygienic environment—damp dwellings, lack of clothing, poor or insufficient food, hard work, care, repeated pregnancies, protracted lactation, or combinations of two or more of these agencies; exogenous agencies of a specific nature—infection, ferments, presence of certain substances in the diet, lack of calcium in the diet, lack of certain vitamines; and endogenous agencies—disturbance of internal secretion, acid formation.

The hypotheses mostly widely accepted for the etiology of osteomalacia are, first, that the actual process is due to the action of an acid, commonly believed to be lactic acid; and second, that the condition is a disease of the ovaries. But there is evidence enough to disprove both of these hypotheses.

Acid Action in Osteomalacia.—The hypothesis, that the disappearance of lime salts from the bone in osteomalacia is due to the action of an acid, is based on the assumption that the process is one of halisteresis, whereby the mineral constituents are dissolved, and the organic matrix of the bone left behind—a hypothesis which falls with the rejection of the halisteresis assumption. Furthermore, we know now that blood and tissue fluids do not become acid, that in the phosphate and carbonate buffer mixtures we have a delicate mechanism for preserving within very narrow limits the neutral reaction of the blood and tissue fluids. But, since the halisteresis hypothesis had an apparent confirmation in the alleged discovery of lactic acid in the bones and urine in osteomalacia, we must examine the evidence on this point. Schmidt states that he found lactic acid in the bones, and Moers and Muck and Langendorff and

Mommsen state that they found this acid in the urine in osteomalacia. These investigators extracted with ether, boiled the ethereal extract with zinc oxid, and, observing rhombic crystals in the dried residue, diagnosed them as zinc lactate. They were not justified in so doing; a number of aromatic acids, whose zinc salts may be confounded with zinc lactate—hippuric acid, for example—may be extracted with ether. By the same method, in fact, Langendorff and Mommsen found lactic acid in normal urine. Neither Schmuzinger, Heuss, nor McCrudden(*e*) was able to find any lactic acid in the urine in their cases. There is, then, no good evidence that lactic acid occurs in the urine in osteomalacia.

Lactic acid has been administered to animals in the attempt to induce osteomalacia artificially. Only Siedamgrotsky and Hofmeister, who fed large amounts of lactic acid to goats, allege any action on the bones. But they obtained no such effect after administration of the much stronger hydrochloric and sulphuric acids, so that if there were any change in the bones in these experiments, the changes were not improbably due to digestive or other disturbances resulting from the large amounts of lactic acid ingested, and not from acid action. Indeed, it requires concentrated lactic acid to decalcify bone in vitro, and it was such acid that Moers and Muck and Henning used to demonstrate that lactic acid will decalcify bone; yet no one can suppose that concentrated lactic acid appears in the tissues. As a matter of fact, according to von Mosetig-Moorhof, even fairly concentrated lactic acid does not decalcify bone; and Heiss, who administered to dogs from two to eight grams lactic acid per day for nearly a year, was unable to observe any effect whatever on the macroscopic or microscopic appearance, or the chemical composition of the bones. Gayet and Bonnet administered one gram lactic acid per day for six months to a female rabbit, who gave birth to a litter of three young during the period. The young, likewise, received lactic acid during the whole period of growth. Neither mother nor young ever showed any evidence of bone disease. More recent experiments (Givens, also Givens and Mendel) have demonstrated that the administration of neither base nor acid has any significant effect on the balance of calcium or magnesium in the body.

A decreased alkalinity of the blood in osteomalacia (by the old titration method) is alleged by Renzi, von Jaksch(*g*), Issmer, Truzzi, and Eisenhardt. Fehling(*b*) and von Limbeck(*a*) found no such decrease in blood alkalinity; and Senator(*g*) found even an increased alkalinity. The alleged decrease in blood alkalinity found by Truzzi persisted even after the patient was cured. As a matter of fact, even a decrease in the alkalinity of the blood or tissue fluids would not make them a better solvent for calcium phosphate; the presence of free acid is necessary. Free acid cannot occur in the blood stream during life; any abnormal acid formed in the metabolism would be immediately neutralized, just as the carbonic

acid, sulphuric acid, phosphoric acid and other continuously forming acid end products of metabolism are immediately neutralized. Furthermore, we know now that we cannot accept the interpretation formerly placed on the results obtained by titration of the blood.

Beck has made determinations of the nitrogen distribution in osteomalacia urine, and his low figures for ammonia show no evidence of acidosis in osteomalacia. Furthermore, osteomalacia does not arise in conditions accompanied by acidosis, severe diabetic coma, for example.

From beginning to end, the evidence that the bone softening of osteomalacia is due to acid action is uniformly negative.

The Relation of the Ovaries to Osteomalacia.—At Porro's suggestion, Fochier of Lyon and Levy of Copenhagen, among others, had carried out supravaginal amputation of the pregnant uterus and ovaries, as a complement to Cesarean section in certain cases of osteomalacia, and noted that the operation had a good therapeutic effect on the disease. As a result, Fochier proposed that this operation be tried in other cases of osteomalacia. Believing that the good effect in these cases might have been due to removal of the ovaries, Fehling(*a*)(*b*)(*c*)(*d*) carried out ovariotomy on a number of patients with osteomalacia. The operation was followed by such good results that Fehling came to the conclusion that osteomalacia is due to pathologically increased activity of the ovaries, leading to stimulation of the vasodilators or paralysis of the vasoconstrictors, followed by congestion and hyperemia of the bones and solution of the bone salts. But even if we admit such bone hyperemia, and a consequent stimulation of bone metabolism, there is no reason to believe it would lead to increased catabolism of calcium, rather than increased anabolism. We need not, however, concern ourselves with these details of the alleged mechanism through which the ovaries control bone metabolism, but only with the larger question of the facts regarding the relation of the ovaries to osteomalacia and bone growth.

The sexual glands have long been supposed to have some control over the metabolism, especially over growth, and over growth of the bones in particular. This supposition is based on common experience in the breeding of cattle and fowl, and on our less complete knowledge of the effect of castration in man, rather than upon controlled laboratory experiments. And some of these commonly accepted facts and conclusions relating to this subject are not justified. The farmer finds, for example, that his castrated male chickens grow larger and fatter than his cockerels. There is no need to assume any direct effect of castration on bone metabolism; the difference can be explained by the more sluggish life of the capon, compared with that of the active aggressive cock. Surgeons very commonly state that women increase in weight after ovariotomy. As a matter of fact, examination of carefully carried out studies on several

series of cases, show a very slight, though probably insignificant, loss of weight (McCrudden(*c*)).

Comparative studies of the fat metabolism, of the storage of fat, and of the amount of oxygen used in cases of normal and castrated animals show no differences. The feeding of ovaries, and ovarian extract, of testes and testicular extract, have given likewise negative results. Complete balance studies, made by McCrudden(*c*) on adult male and female dogs, before and after castration, show no effect on the metabolism of nitrogen, sulphur, calcium, magnesium, or phosphorus. Less complete metabolism experiments on puppies, and comparative studies of the total amount of phosphate in normal and castrated animals, have given likewise negative results.

Furthermore, histological examination of the ovaries in osteomalacia shows no changes. A number of such ovaries have been examined. Bulius made a careful study of six cases and found no change. He was obliged to reject findings, reported in an earlier paper of his own, in which he alleged hyperemia and hyaline degeneration of the arterial walls.

In this connection, too, we think of the cases of osteomalacia in young women before the ovaries have begun to function, in old women after the menopause, and especially in men. Such cases as the latter, though rare, do occur. One of the bones analyzed by McCrudden came from a young man with the disease. Among 360 cases of osteomalacia reported by five writers, there were thirty-nine cases of the disease in men (McCrudden(*e*)). Without making a special search for all cases, McCrudden(*e*) found ten cases of the disease reported during the last twenty-five years in childless, unmarried women—the diagnosis being confirmed in some cases by autopsy—and nine cases in men, four of which were confirmed by autopsy. I have seen two cases in childless, unmarried women, and two cases in men.

The temporary nature of the good results of castration on the clinical course of the patient studied by McCrudden led to a careful examination of the literature to see how frequently this operation resulted in permanent cure in other cases(*e*). An examination of the clinical results of castration in osteomalacia naturally began with the cases of Fehling. By 1895, the date of his last report, Fehling had reported fourteen cases of osteomalacia treated by castration(*d*). Of these, but six were well three years after the operation. Two were not cured, and one of them, after showing temporary improvement, later, as in McCrudden's case, then relapsed. The others either died or could not be traced. Von Winckel has reported three cases, of which one was improved after castration. Polgár tried the operation in six cases; a cure followed in all but two. Wheaton, Latzko, and Poppe have each reported one case, in which castration was carried out without any effect on the disease. In one of two cases, Neumann(*b*) failed to help by cas-

tration. Truzzi reported ninety-seven cases of osteomalacia treated by castration. Seventeen per cent of the patients were not cured. These results have not been selected to show that castration is not always followed by cure, but include most of the results reported in the literature. Most of these patients were not cured by castration, and most of those called cured were not followed for any length of time. The longer such patients have been followed, as in the cases of Fehling and McCrudden, the smaller the proportion of cures. A case, reported by Hofmeier, illustrates this point very well. In 1891 he reported a case of non-puerperal osteomalacia cured (followed only for three months) by castration. No further report of the case appeared in the literature, but many years later I became acquainted with Professor Hofmeier, who told me that the patient soon relapsed.

The evidence, then, is strongly against the hypothesis that osteomalacia is a disease of the ovaries. The supposed beneficial effect of castration on puerperal osteomalacia is easily explained. It is usual for osteomalacia to improve after the end of pregnancy and lactation, and only relapse again during a subsequent pregnancy. If there is no subsequent pregnancy, there is no relapse.

Need of Calcium as a Cause of Puerperal Osteomalacia.—If we bear in mind the facts already pointed out regarding the active nature of bone metabolism, we see one direction in which to look for the cause of osteomalacia. When the necessity of any food material is increased without a corresponding increase in the supply, or when the supply is decreased, as in starvation, the stores of that substance in the body are mobilized. We are familiar with this process in the case of glycogen and fat metabolism; and evidence that the same thing occurs in the case of the mineral constituents of the bones has been pointed out in the section on normal metabolism. The periods of life during which the need for calcium is greatest are (a) during pregnancy and lactation, when there is a flux of calcium to the growing fetus and to the milk; and (b) during the period of bone calcification in young children. And it is precisely at those periods (the exceptions will be taken up later) that rickets and osteomalacia occur.

The following calculation indicates what a large amount of calcium must come from the skeleton of the mother during the later stages of gestation. According to analyses made by Michel, on the average, a seven months human embryo weighs 1024 grams and contains 0.8 per cent (8.2 grams) CaO; a full term fetus weighs 3335 grams and contains 1.4 per cent (46.7 grams) CaO. This indicates a gain of 38.5 grams in sixty days or 0.64 gram a day, which is more than twice the average daily retention of calcium (Hoffström). The figures are only rough approximations, but they indicate that considerable quantities of calcium must be transferred from the bones of the mother to the growing embryo.

Calcium balance experiments on milking cows indicate that the same kind of flux from the bones takes place during lactation (Forbes, Beegle, Fritz, Morgan and Rhue(*a*)(*b*)).

As to the great need of lime salts during infancy, observation shows that, weight for weight, a five months old infant requires from two to five times as much calcium as an adult.

A factor contributing to the decalcification of the skeleton at times when there is a need of calcium elsewhere in the body is the ease of bone catabolism compared with difficulty of bone anabolism. This is shown by the fact that when there is a negative calcium balance, as in lactating cows, it seems impossible to change this into a positive balance by the administration of calcium salts. The bone readily gives up its calcium but, even when its calcium store is somewhat depleted, does not readily lay on new calcium (Forbes, Halverson and Morgan).

As further chemical evidence in this direction, regarding calcium metabolism during pregnancy, we have the observation of Neumann (*b*) showing a retention instead of a loss of calcium, in a patient with osteomalacia during pregnancy; there was also a retention of phosphate. In this case calcium phosphate was leaving the skeleton, but, since it was going to the fetus, it did not show up as a negative balance. (Table 26.)

TABLE 26

CALCIUM AND PHOSPHATE BALANCE DURING PREGNANCY

	CaO Grams	P_2O_5 Grams
In food	12.40	14.70
In excreta	9.97	13.26
Retained	2.43	1.44

That a healthy fetus can develop in a woman who has osteomalacia, and who is not, therefore, without severe consequences to her own tissues, in a condition to give up lime salts is not surprising, in view of the results of Jaegeroos, who showed in experiments on dogs that a fetus can develop at the expense of the mother even when there is a negative phosphorus, nitrogen, and salt balance in the metabolism of the mother. And Dibbelt showed that puppies can develop normally in utero, while the mother lives on such a low calcium diet as to produce osteomalacia. That is to say, when there is not enough material in the food for the mother alone, the fetus continues to grow, and the growth is at the expense of the tissues of the mother, even if she is not in a condition to give up material.

Histological investigations, too, are in agreement with the chemical in indicating a flux of calcium salts from the bones of the gestating mother. Thus Hanau found changes similar to osteomalacia at post-

mortem examination of the bones, especially the pelvic bones, of twenty pregnant women who, during life, were apparently free from any symptoms of the disease.

Clinical evidence, too, points in the same direction. Fehling(*b*) has observed that many women who have several quickly succeeding pregnancies have the subjective symptoms of osteomalacia—pain and tenderness in the pelvic bones—without the deformity observed in undoubted osteomalacia, and has suggested that these are mild cases of the disease.

Careful examination by McCrudden(*e*) of the clinical histories of as many cases of osteomalacia as could be found in the literature brought out certain clinical facts in harmony with the chemical and histological findings which are not emphasized in the text books: In the first place, osteomalacia rarely begins in the first, or even in the second pregnancy, but usually after several rapidly succeeding pregnancies, and, furthermore, is usually seen only in poor women whose hygienic environment is bad. As a rule, the first attack appears during the later months of pregnancy and the patient recovers after parturition. A second attack may not occur. But if pregnancies succeed each other rapidly, other attacks occur, and the succeeding attacks begin earlier and earlier in succeeding pregnancies, are more severe, and last longer after the pregnancy is ended, until finally there is no longer any recovery. In other words, it is only after a long continued and severe drain on the bones of a poorly nourished patient that the body fails to respond to the demands on it, and even then recovery follows if the severe demands are not continued. Of course, not every case runs like this, but this is the typical course of the disease.

These clinical features seemed so important and suggestive that a search was made to see if other investigators had not made similar observations. As early as 1829 (Kilian), it was observed that osteomalacia occurs chiefly in women who have been pregnant many times in rapid succession; and in 1857 Kilian pointed out that puerperal osteomalacia tends to recovery, only to undergo exacerbation during a succeeding pregnancy. Numerous other writers have since called attention to these facts, Senator(*c*), Cohnheim(*b*), Latzko, Sternberg(*a*), Everke, Zesas.

The observation made by Cohnheim(*b*) and by Zesas that fractures during pregnancy are slowly repaired (a proper callus is formed with difficulty), is a point in favor of the theory that a flux of calcium from the bones to the growing fetus is responsible for puerperal osteomalacia. Sufficient lime salts needed for callus formation are not available.

Chemical, histological, and clinical evidence, then, are in accord, and in harmony with the view that osteomalacia is but an exaggeration of the increased metabolism of the bony tissues in pregnancy. Normally, the anabolic and catabolic processes in the bones balance each other. In pregnancy, as a result of increased needs of the fetus for lime salts,

the apposition of new salts to the bones may not make up for those removed, and the newly laid down bones becomes poor in lime salts. If the deficiency in lime salts is great enough and extensive enough, the bones will become soft and fragile. In other words, in osteomalacia we are dealing with extreme grades of a normal process.

The reason that castration has been followed by beneficial results in many cases of puerperal osteomalacia is simple enough. A great many different kinds of treatment besides castration are followed by either temporary or permanent cure. Thus, chloral (Petrone), sulphur baths (Latzko, Weisz), chloroform narcosis (Petrone), and especially phosphorus (Sternburg(*a*), Höxter, Siegert, Bernstein(*a*)) have been followed by good results. The cures following injection of adrenalin have led Bossi to the conclusion that osteomalacia is a disease of the suprarenal glands. Good hygiene alone is very effective. And, as already pointed out, the condition shows a natural tendency to cure, following termination of pregnancy and lactation. On the other hand, all these measures, including castration, sometimes fail. It is to be noted that the cases of osteomalacia cured by castration are cases of puerperal osteomalacia. No case of non-puerperal osteomalacia permanently cured by castration is on record in the literature. The important feature of castration in making a cure permanent is that, once cured, the cause of a future relapse—pregnancy—is made impossible.

A good example of the beneficial effect of castration is seen in a case reported by Neumann(*a*). The patient had some symptoms of osteomalacia during her seventh and eighth pregnancies but recovered. The disease came on again during her ninth pregnancy. The ninth child was born January ninth; the patient began to show improvement by March first; by April first she was fairly well recovered. Osteomalacia came on again during her tenth pregnancy. At this time Neumann removed the uterus and adnexa, and the result was a permanent cure.

Summary: Puerperal Osteomalacia.—To summarize briefly the etiology and nature of the process in osteomalacia: Just as the subcutaneous fatty tissue acts as a store of fat, and the liver glycogen as a store of carbohydrate, so the skeleton acts as a store of calcium salts, to be called on in time of need. During the later months of pregnancy and during lactation, the need for calcium salts is great, greater than the intake in the food, and it becomes necessary to draw upon the calcium supply in the bones. The result is that the new bony tissue laid down to replace old bone as it disappears is poorer in lime salts than the normal. Ordinarily the quantitative change in the composition of the bones is not great enough to produce symptoms. At the end of gestation and lactation, when the extra need for calcium has ceased, normal bone is again laid down. The calcium content of the bone becomes low enough to induce symptoms of osteomalacia only when, as a consequence

of several rapidly succeeding pregnancies and periods of prolonged lactation, the loss of calcium has been very great. Even then the tendency is to recover, and unless a new pregnancy supervenes before recovery takes place, such recovery may be permanent. But if each new pregnancy, with its consequent need for calcium, comes on before the bones have made up previous losses of calcium, osteomalacia may become permanent. And finally, the decrease in the calcium phosphate content of the bone becomes so great that it is beyond the power of the body to increase anabolic processes to such an extent that they will not only balance the increased catabolism, but make up also for earlier losses. An exam-

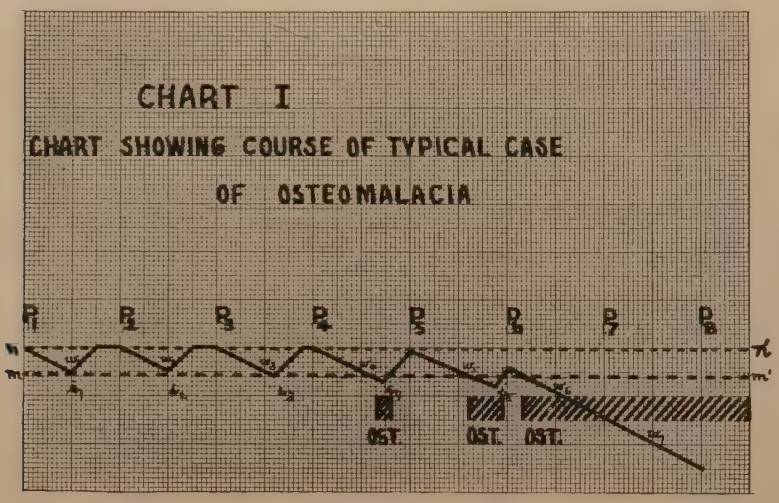


Chart 1.

ple of the disease showing the typical course and final cure by castration is seen in the case of Neumann, referred to a few paragraphs back.

We may represent a case of the disease showing the typical course in chart form.

The abscissæ represent time, the ordinates represent amount of calcium in the bony system. P_1 P_2, etc., represent the beginning of pregnancy; W_1 W_2, etc., represent the end of pregnancy and lactation (weaning), i_1 i_2 represent the beginnings of improvement. The line n–n′ represents normal calcium content in the bones; the line m–m′ the amount of calcium in the bones, below which symptoms of osteomalacia appear. The crosshatched areas represent periods of osteomalacia. In this imaginary case, there is a short, mild attack during the fourth pregnancy from which the patient completely recovers, next a somewhat more severe attack during the fifth pregnancy from which the patient likewise recovers, but not to a completely normal condition. Osteomalacia again returns early in the sixth pregnancy and remains permanent. The lengthening

of the period between weaning and beginning improvement (w to i) in succeeding pregnancies is referred to later on.

Etiology of Other Disturbances of Bone Metabolism.—In puerperal osteomalacia the bone changes are greater than in other forms of disturbed bone metabolism; the cause of the disturbance is more apparent; and it has been more thoroughly studied. It serves, therefore, as the best type in discussing pathological bone metabolism. But other forms of disturbed bone metabolism fit, quite properly, into the theory of bone metabolism outlined here. Causes other than pregnancy and lactation may be responsible for a drain of calcium from the bones, and result in osteomalacia. Henning, and more recently Berger(*b*), have pointed out that the formation of lime stones, especially in the kidney, is a very common accompaniment of osteomalacia. These kidney lime stones are so large and so common in such cases that the condition has been named calcareous metastasis (Boulby). In one such case reported by Daires-Colley in a ten year old girl, the renal calculi were so large and abundant as to lead to suppurative pyelitis and eventually death. Softening of the bone has been observed at autopsy to accompany calcification of the muscles in myositis ossificans progressiva (Mays, Rabeck). More recently röntgenographs have shown rarefaction of the bone in this disease (Krause and Trappe). A case of ostitis rarificans has been reported by Jadassohn following calcification in the papillary muscles, kidneys, lungs, spleen, skin.

Decalcification of the bones (shown by bone analysis) results in cases of obstructive jaundice from the need of calcium salts to neutralize the toxic effects of the bile acids (King, Bigelow and Pierce). Osteomalacia appears, too, in animals, especially dogs, with permanent biliary fistula as the result of the loss of calcium salts (von Recklinghausen(*c*), Looser(*b*), Seidel, Lenormant). The fact that fractures in such cases heal with osteoid tissue, and not real bone, is in harmony with the theory of bone metabolism outlined in this chapter, and lends further weight to it.

Etienne and Duplain(*a*)(*b*) have noted a connection between osteomalacia and severe arteriosclerosis. They report the case of a woman with very marked arteriosclerosis and with a large calcified myoma, in whom the osteomalacia came on just after the arteriosclerosis. The decalcification in this case was greatest in the vertebræ at the level of the most intense calcification of the aorta. These writers point out that the calcium content of the bones of old people with severe arteriosclerosis is less than that of other old people.

Trevelyan has observed that osteoporosis sometimes accompanies the increased bone formation in acromegaly.

In one case reported by McCrudden, the flux of calcium was apparently induced by the growth of bony tumors (McCrudden and Fales(*a*)). An extract from the history and two röntgenographs from this case follow.

Fig. 1 shows one of the bony tumors. Fig. 2 shows an example of the rarifaction of the bone.

The patient, an unmarried woman of forty-two, dates her illness to 1891, when she noticed a hard, painless nodule about the size of a bean on the right side of her lower jaw. Six months later, the growth, which had by then increased to the size of a hen's egg, together with a piece of the jaw, was removed. In 1895 she began to have difficulty in walking; her ankles would "bend in and out on walking, as if they were made of

Fig. 1.

rubber." In the fall of the year, small, hard painless nodules were noticed on her shin bones. The largest, on the left, was about the size of a walnut. In 1898, while riding on a tricycle, she fell and fractured her right thigh, but it caused her very little pain. During the seven weeks that she was laid up with this fractured thigh, she had an attack of renal colic, and three weeks later passed several small, gray stones. At intervals of six to eight months for the next six years, she had attacks of renal colic; and about three weeks after each attack she would usually pass a stone about the size of a pea. Since about 1905, a hard, painless growth near the lower edge of the spine has been gradually enlarging. In 1908, a bony growth, which has since caused difficulty in breathing, appeared in the right nostril. In 1909, she noticed small, hard nodules on her forehead. About this time, in shaking hands with a friend, the second metacarpal bone of the right hand became fractured. In August, 1910, while washing her hands, she dislocated the terminal phalanx of the left index finger. By 1911, she had become bedridden on account of increasing stiffness and weakness. At this time she felt pain only when moving about or being handled.

Physical examination of the bony system showed the following: A slight ridge can be felt extending along the suture lines of the skull. There is a hard nodule about the size of a pea on the temporal bone behind the right ear, an indefinite firm swelling behind the left ear, and three small, firm nodules on the frontal bone. There are two firm swellings on either side of the raphe, between the hard and soft palate. There is a sharp, bony exostosis on the outer side of the outer third of the right clavicle. There is a marked rosary. At the left, over the costochondral margin, there is tender elevation. There is moderate kyphosis of the cervical and upper dorsal vertebræ and marked scoliosis. The sacrum is very prominent. The iliac wings are thick-

Fig. 2.

ened and nodular. The left leg is somewhat longer than the right, owing to bowing out of the right femur, just above the middle (the site of the old fracture, over which is a large callus). The surfaces of both shins are roughened. Just below the middle of the left tibia, and involving chiefly the inner surface, is a hard, oval, bony mass 11 cm. long and 13 cm. wide. On the second metacarpal joints of both hands, there are hard swellings. These bony masses and nodules are not tender.

Röntgenograms show scattered areas of bone rarefaction in different portions of the skeleton.

Osteomata and calcification of various tissues are not uncommon occurrences. Buerger and Oppenheim have pointed out that heteroplastic bone formation in the dura, pia, arachnoid, muscles, bladder, scars,

lungs, pleura, eye, stomach, liver and lymph nodes is fairly common. In twenty-nine cases of metastatic bone formation reported in the literature, some extensive destructive disease of bone was demonstrated in all but four (McCrudden(*f*)); and it is very probable that a systematic search such as Hanau made for evidences of osteomalacia in the bones of pregnant women would disclose evidence of mild grades of osteomalacia in all these cases.

A diet deficient in calcium can give rise to osteomalacia. The first experiments in this direction were undertaken by Chossat(*a*) in 1842. Chossat fed pigeons a diet, poor in calcium salts—wheat, well extracted with water. After some months the bones of the pigeons became fragile, and at autopsy the normal bone was found to be replaced in part by a kind of soft cartilaginous material. On the same diet plus calcium carbonate the pigeons remained well. Nearly twenty years later, Edwards who repeated these experiments, obtained the same results.

A diet deficient in calcium is especially effective in causing bone diseases when the need of the body for calcium is great—during the growing period and during pregnancy. In 1875, Roloff(*a*) observed that young dogs and swine kept on a diet deficient in calcium salts developed rickets. Voit developed rickets in a growing dog by administering a calcium-poor diet; a control animal receiving the same diet with the addition of bone ash did not develop rickets (Voit(*a*)). Stoetzner and Salge carried out substantially the same experiment as Voit with the same result. In 1879 Roloff(*b*) kept a sheep during the whole period of pregnancy and lactation on food from which the calcium salts had been dissolved out with hydrochloric acid. The animal developed severe osteomalacia, the diagnosis being confirmed at autopsy. In the same way Dibbelt, and also Stilling and Mering produced osteomalacia in pregnant dogs. More recently Weiser(*b*) selected six young pigs of the same age and race, and to three of them administered a diet poor in calcium while to the other three he administered a diet containing an abundance of calcium. Bone analysis showed a much lower calcium content in the set whose diet was deficient in calcium.

A deficiency of calcium in the diet is often responsible for spontaneous osteomalacia in animals. This disease, referred to as *malnutrition of the bones* by veterinarians, occurs in oxen, cows, horses, sheep, goats, swine, dogs, rabbits and rats. It is especially common in parts of France, where it is called *cachexie osseuse* or *maladie des pattes;* in swine it is called *maladie de gouttes,* and in horses *maladie du son* (Badolle). The disease occurs also in the United States, especially in southern Alabama, in western Washington, and in parts of Mississippi and Florida. In the sections of Alabama and Washington where the disease is prevalent the soil is very poor in lime (Forbes, Halberson and Morgan).

The disease appeared in almost epidemic form in the Saxon Erzegebirge in 1909-1910; analysis of the hay eaten by the horses showed an extremely low calcium content (Schennert, Schattke, Lötsche). The losses of calcium through excessive lactation in cows is very great (Meigs, Blatherwick and Gary, also Forbes, Beegle, Fritz, Morgan and Rhue(*a*) (*b*)), and if upon this are superimposed other unfavorable conditions—unfertile, sandy soil, granitic soil, insufficiently fertilized soil, season of drought, overstocked pastures, deficient food supply—malnutrition of bone may develop. The animals suffering from this condition readily respond to improved nutrition, especially if bone meal or chalk be added to the diet (Forbes, Beegle, Fritz, Morgan and Rhue(*a*)).

What has been said about the cause or causes of calcium inadequacy in non-puerperal osteomalacia applies to rickets, osteitis deformans and other forms of disturbed bone metabolism. Many different factors may contribute. A survey and analysis of all the conflicting evidences on the subject, especially in the case of rickets, would be out of place here. The important fact to bear in mind is the active and continuous nature of bone metabolism. It is then easy to understand that different factors may contribute to the depletion of the calcium store in the bones.

The same kind of factors which produce osteomalacia in adults may give rise to rickets in children. Pregnancy and arteriosclerosis do not of course come into consideration in the case of rickets, but renal calculi do, as already pointed out (Daires-Colley), and myositis ossificans progressiva, which in adults may give rise to osteomalacia, may be accompanied in childhood by rickets (Rabek). Eustace Smith has pointed out that in rickets the process of ossification is not only retarded; it is also perverted; calcium salts are deposited in abnormal situations (Smith). The muscles especially seem to be a storing place for calcium in rickets. Pritchard has described in some detail how rickets develops as the result of a need for calcium more urgent than that of the calcifying bones.

Dr. Charles F. Painter, the Boston orthopedic surgeon, has called my attention to the occurrence of a late variety of non-rachitic bow legs, occurring in children about the time the epiphyses begin to harden; the flux of calcium to the hardening epiphyses may be responsible for the decalcification elsewhere.

Osteitis deformans occurs late in life, and is undoubtedly a localized form of osteomalacia. It is practically always accompanied by arteriosclerosis (Higbee and Ellis; Emerson). In such cases the areas of bone rarefaction and intense arterial calcification can be seen side by side in skiagrams. Here again we have a demand for calcium (on the part of the arteries) followed by a loss of calcium by the bones.

Careful examination of the bone in osteogenesis imperfecta has shown that the process is of the same nature as that in osteomalacia; in this

connection too the soft bone is newly formed bone, poor in lime salts (Eiken).

How widely different the nature of the factors responsible for abnormal bone metabolism can be, may be judged from the fact that apparently reliable evidence involves not only pregnancy, but also bacterial infection, glands of internal secretion, arteriosclerosis, certain foodstuffs, absence of vitamines, and starvation, or undernutrition.

Montpurgo, de Sant Agnese, and Arcangeli, in Italy and Moussu and Charrin, in France, have demonstrated the presence of a transmittable infectious agent in osteomalacia and rickets. These investigators were able to transmit the disease from one animal to another, and the essential identity of rickets and osteomalacia is indicated by the fact that the same organism produced either rickets or osteomalacia according to the age of the infected animal.

As to the glands with an internal secretion, practically every one of them has, at one time or another, been alleged as having something to do with calcium metabolism or with osteomalacia.

The case for the ovaries has already been discussed.

More recently, much has been written to show that osteomalacia is a disease of the adrenals. But the evidence has all been based on the supposed curative effect of adrenalin in osteomalacia. The first to suggest this etiology was Bossi, an Italian physician who, beginning December 16, 1906, administered epinephrin for four successive days to a patient with osteomalacia. At the end of that time the patient had much less pain and was, therefore, discharged as cured. *Within four weeks of the first treatment,* the published results appeared. (Bossi: "Nebenniere und Osteomalakie." *Centralbl. f. Gynäk.,* Jan. 19, 1907, p. 69.) A number of other just such "cures" have been reported in the literature. In all cases, the "cure," reported soon after treatment, meant simply relief from pain. It is a well known fact that even without any treatment, tenderness and pain rapidly disappear at times in osteomalacia; such temporary relief does not indicate cure. The case reported by Kaessman may indicate what happens in such cases. Kaessman administered epinephrin daily, from September sixth to September eleventh, 1907. On September fourteenth the patient was sent away better, with instructions to keep up the treatment, only to return nine days later, worse than ever.

The evidence connecting osteomalacia and the thyroid gland is even less convincing, if possible, than that connecting osteomalacia and the adrenals. Hoennicke(*a*)(*b*), who first suggested that osteomalacia is a disease of the thyroid, refers to the similarity in geographic distribution of osteomalacia and recognized diseases of the thyroid, such as myxedema and Graves' disease, and to the similarity in incidence, with reference to age, sex, and gravidity. Hoennicke further asserts that he

provoked osteomalacia in a pregnant rabbit by administration of thyroid gland. Told and Sarvarat report one patient with both osteomalacia and goiter, and have found eleven similar cases in the literature. Such evidence is not very convincing. That there is a relationship of some sort between bone metabolism and the thyroid gland is evident from the failure to grow, and the delayed ossification (Schmidt) in cretinism, the failure of normal skeletal development in thyroidectomized animals (Biedl), and the more rapid bone formation and increased calcification in thyroidectomized animals, to whom thyroidin has been administered (Bircher).

A relationship between the hypophysis and osteomalacia has been assumed on the basis of results of pituitrin therapy in this disease (Bab, Neu; but the evidence is poor. The clinical changes in acromegaly, especially the increased bone formation, and the osteoporosis which sometimes accompanies it (Trevelyan), indicate a relationship of some kind between the hypophysis and bone metabolism. What little we know of this subject is fully discussed in the chapter on the hypophysis.

There appears to be a relationship of some sort between bone metabolism, and calcium metabolism, and the thymus. It has been observed that thymectomy decreases the calcium content of the bone (Klose and Vogt), increases the calcium excretion (Fränkel(*b*)) and makes the bones soft, flexible, and fragile (Basch, Klose(*a*)(*b*), Soli).

The evidence connecting osteomalacia with the parathyroid glands is the result of studies carried out in Professor Weichselbaum's laboratory in Vienna, and is stronger than that connecting the disease with any other gland. Erdheim(*a*) examined the parathyroids in six cases of osteomalacia, and found pathological changes in five of them. Todyo found pathological changes in these glands in seven cases of osteomalacia, and in eleven cases of osteoporosis; as controls he examined also the glands in twenty-four cases of other kinds of disease. In the same laboratory, in carrying out postmortem examination of a patient, who showed no symptoms of osteomalacia during life, Bauer discovered a small tumor of the parathyroid, and this led him to make a special examination of the bones for evidence of osteomalacia. Osteomalacia was present. Very thorough experimental studies were then undertaken in animals, and it was found that in parathyroidectomized rats callus formation after fracture is delayed (Erdheim(*b*)).

It was found further, that the incisor teeth of rats grow fairly rapidly, the dentin and enamel being laid down in layers (Erdheim(*c*)). In cases of spontaneous rickets in these animals, a failure of calcification of the dentin and enamel accompanies the rickets (Erdheim(*b*)). Examination of the growth and calcification of the teeth gives, therefore, a fairly precise estimate of the duration and extent of any disturbance of calcium metabolism. After removal of the parathyroids, the dentin and

enamel laid down is free from calcium (Erdheim(*c*), Toyofuku). If the extirpated parathyroids are transplanted into the abdominal wall of the same animal, layers of uncalcified dentin are laid down until the transplanted parathyroids begin to function in their new location, when normal dentin is again laid down (Erdheim(*d*)).

The evidence connecting parathyroid tetany, with disturbance of the calcium metabolism is discussed in another chapter of this work (see Parathyroids).

Oxalic acid or oxalates in the food give rise to a negative calcium balance and lead to osteomalacia. In 1881 the number of cases of osteomalacia in cows who were eating large quantities of beet tops in a certain part of Germany, led to an investigation which showed that the beet tops contain an abundance of oxalic acid (Haubner). Experiments showed that administration of oxalic acid, or oxalate in the food, leads to a negative calcium balance in rabbits (Caspari, Luithlen), sheep (Zuntz (*b*), von Nathanius), dogs (Caspari), and guinea pigs (Sarvonat and Roulier); a decrease in the calcium content of the bones (Caspari, von Nathanius, Zuntz(*b*)). The administration of sufficient calcium carbonate offsets the action of the oxalic acid or oxalate, so that there is neither a negative calcium balance (Zuntz(*b*), von Nathanius), a loss of calcium from the bones (Caspari), nor osteomalacia (Caspari).

In this connection it is interesting to note that osteomalacia can be induced in rabbits by the injection of lactose (Bonnamour, Badolle and Escallon) or glucose (Parisot, Badolle, Robert and Parisot). The osteomalacia resulting from glucose injection is accompanied by oxaluria, and the severity of the disease is proportional, not to the amount of glucose injected, but to the intensity of the oxaluria (Parisot).

Calcium oxalate is an insoluble substance, which is formed wherever calcium and oxalate come together in alkaline, neutral, or even slightly acid solution. It is, therefore, quite probable that oxalate precipitates, or at any rate renders physiologically inactive, any calcium salts which the oxalate meets in the body; and that the flux of calcium salts from the bone is the result of an attempt to supply the resulting deficiency. An indication in this direction is given by the experiments of Chiari and Froelich(*b*), who found that the administration of sodium oxalate overcomes the inhibiting effect of vagus stimulation on the heart. In the belief that this oxalate action might be due to the precipitation or inactivation of the calcium in the tissues, these investigators administered calcium salts intravenously and restored normal condition. Chiari(*a*) demonstrated also that oxalates have a similar action on the calcium of the cells of the gastro-intestinal tract; the calcium is precipitated and thereby inactivated, leaving a preponderance of sodium salts whose stimulating effect causes increased peristalsis.

Since I came across the literature connecting osteomalacia with oxalic

acid, I have seen three more cases of osteomalacia, all of which showed a great abundance of calcium oxalate crystals in the urine. In a recent report of a case of osteomalacia by Freund and Lockwood, mention is made of the great abundance of calcium oxalate crystals in the urine. Furthermore, as already pointed out, renal calculi are a very frequent accompaniment of osteomalacia (Henning, Berger(*b*), Daires-Colley), so frequent indeed that the combined condition has been referred to as calcareous metastasis (Boulby); and renal calculi almost always consist of calcium oxalate.

Numerous papers dealing with the relation of vitamins to bone metabolism, especially in rickets, are appearing in the current medical journals, but it is too early as yet to appraise the results.

The numerous references to osteomalacia in the German, Austrian, Dutch, and Danish medical journals of 1918 and 1919, testify to the increase in the number of cases of this condition as the result of the food shortage. The increased incidence affected not only man, but also the domestic animals. It is so closely associated with lack of food that it is sometimes referred to as "Hungermalazie," or "Hungerosteomalazie" (Schlesinger(*a*)(*b*)).

Certain types of dwarfism and infantilism are undoubtedly the result of imperfect bone metabolism, or, as any rate, closely associated with imperfect bone metabolism (McCrudden(*f*)). These conditions are considered elsewhere in this work (see Infantilism).

Overproduction and Bone Disease.—It must be apparent from what has already been said that osteomalacia, rickets, and similar pathological conditions of the bone are to be regarded not as specific diseases, but rather as syndromes resulting from a considerable exaggeration of a normal condition. The calcium of the bones acts as a reservoir of this element to be drawn on in times of need, and consequently the total calcium content of the bones, as well as the percentage of calcium in the bones is normally subject to certain variations. A considerable fall in the calcium content of the bone makes the bone soft and fragile. Such a fall in the calcium content of the bone may be brought about by a variety of causes. When the cause ceases to operate, rapid restoration of the bone to the normal is the rule. But, as in other physiological processes, there is often or always a kind of "overproduction," a continuance of the process for a time after the original stimulus has been withdrawn, a lag in the return to normal. And this "functional inertia" plays a certain part in the production of some cases of osteomalacia.

Consider tables 27, 28, and 29, giving summaries of the metabolism of one of McCrudden's cases, in three different phases of the disease in one patient (McCrudden(*b*), also Goldthwait, Painter, Osgood and McCrudden).

TABLE 27

METABOLISM DURING ACTIVE STAGE OF OSTEOMALACIA (8 DAYS)

	CaO Grams	MgO Grams	P_2O_5 Grams	S Grams	N Grams
Intake	4.56	2.207	12.05	7.15	69.12
Outgo	5.66	2.015	12.37	2.68	63.02
Retention	....	0.192	.....	4.47	6.10
Loss	1.10	.....	0.32	....	.....

TABLE 28

METABOLISM DURING STAGE OF BEGINNING IMPROVEMENT IN OSTEOMALACIA

	CaO Grams	S Grams	N Grams
Intake	10.03	10.54	127.0
Outgo	7.20	4.84	104.3
Retained	2.83	5.70	22.7

TABLE 29

METABOLISM DURING STAGE OF BEGINNING RELAPSE IN OSTEOMALACIA (6 DAYS)

	CaO Grams	MgO Grams	P_2O_5 Grams	S Grams	N Grams
Intake	3.44	1.504	12.28	2.897	38.85
Outgo	8.27	1.764	10.35	2.793	34.68
Retained	....	.....	1.93	0.104	4.17
Loss	4.83	0.260	.....	.....	.....

The figures shown in Table 27 give the results obtained during the active stage of the disease. There is a loss of calcium and a retention of magnesium and sulphur.

The figures shown in Table 28 give the results obtained in a metabolism observation made just as clinical improvement began. Coincident with the clinical improvement was a retention of calcium. But retention of large quantities of sulphur still persists for a time after improvement in the calcium metabolism has begun.

The figures shown in Table 29 give the results obtained just at the beginning of a relapse. The negative calcium balance is well marked. But magnesium retention had not yet begun, and the sulphur retention had scarcely begun.

Still better examples of "overproduction" are those cases of osteomalacia in which the flux of calcium is started by a need of calcium within the body. Such a case is the one described by McCrudden, the clinical history of which is summarized earlier in this chapter. In that case, the flux of calcium seems to have been started by the growth of bony tumors. The loss of calcium was eventually greater than the need, and led eventually to a negative calcium balance. Berger(*a*)(*b*) refers to two cases

of osteomalacia following osteotomy in which the flux of calcium was started by the need of the repairing bone. In one of these cases the loss of calcium finally ran up to 9.0 grams a day—an enormous amount. Thieme cites two cases in which the osteomalacia was the result of the flux to repair a broken bone. And in the discussion of Thieme's paper, Liniger of Bonn cited another similar case.

There are many analogies for this process of "overproduction." The best example is probably that of the continual production of free receptors which, according to the theory of Ehrlich, explains acquired immunity in such cases as diphtheria and smallpox. Indeed, Weigert has pointed out that overproduction is characteristic of all tissue repair. Harris has written a book on the property which he calls "functional inertia," and has pointed out that the property is as fundamental an attribute of living matter as irritability itself. He defines functional inertia as "that property of protoplasm whereby living matter contrives to remain in a functional *status quo ante,* notwithstanding that it has received a stimulus, or, having responded to a stimulus, it contrives to exhibit its functional activity for a certain time after the stimulus as a form of energy has ceased." The condition may be compared with a heavy door, which, when at rest, requires a certain time to get into full swing after it has been pushed, and, when moving, takes time to stop if held. Of examples of latent period in starting activity, there is the latent period of muscular contraction, that, occurring after glands are stimulated through their nerves, and before they begin to secrete, and that, occurring before the heart beat begins to accelerate its rate when the augmentor or accelerator nerves are stimulated. Of examples of continued activity may be mentioned the continuation of accelerated heart action for a time after stimulation of the augmentor nervous apparatus has ceased. It is not impossible that another example of such overproduction or functional inertia is the change in the metabolism brought about by morphinism, which enables the body to destroy increasing amounts of morphin, but which continues and has a damaging effect on the body itself, if the drug is suddenly withdrawn. Overproduction is probably another example of the factors of safety with which, as Meltzer has pointed out, the body is so well endowed.

The occurrence of attacks of osteomalacia, earlier and earlier, in succeeding pregnancies, and the increasing severity of subsequent attacks, make one think of the more severe and rapid production of symptoms of certain diseases; e. g., serum disease and others after a previous inoculation—a kind of allergy (von Pirquet(*b*)), or, to put it still more broadly, "a cell stimulated to perform a certain act not only continues to perform that act for some little time after the stimulus has ceased, but, what is more, on a second occasion a slighter stimulus will induce the like series" (Adami).

The theories of functional inertia and allergy cited here are, of course, not used as arguments in favor of the conception of normal and pathological bone metabolism outlined in this chapter. This conception is based upon the facts observed in chemical, clinical, and anatomical investigation. The analogies are cited merely to show that, in all probability, the process in osteomalacia is but a special example of certain more general laws governing the *modus operandi* of living matter.

II. Diseases of the Joints

For practical use in discussing the metabolism, the principal chronic arthropathies may be classified as follows:

1. True gout.
2. Trophic arthropathies secondary to disease of the central nervous system.
3. Arthropathies secondary to infections.
4. Primary hypertrophic arthritis.
5. Primary atrophic arthritis.

Only a relatively small proportion of chronic arthropathies are seen that cannot be easily classified according to this scheme: (a) those cases that do not appear to come under one of these headings at all; (b) those cases which it is difficult to classify. Most of the difficulty arises from the fact that some cases of atrophic arthritis in the early, active stages resemble certain forms of the infectious type of arthritis. If these cases are followed long enough, the course of the disease usually shows whether they belong in class 3 or class 5.

The metabolism in the *first type* of arthropathy—true gout—is discussed elsewhere in these volumes.

The metabolic disturbances in the arthropathies of severe nervous disease, the *second type,* affect chiefly the bone adjacent to the articulating surfaces proper. In the section on bone metabolism it is pointed out that bone is continuously undergoing metabolism, that old bone is continuously being absorbed and new bone laid down, and that the new bone laid down may not exactly resemble the old either in chemical composition, density, or architectural structure. When there is a great need of lime salts in other parts of the body, there may be a change in the chemical composition of the newly apposed bone; it may become poor in calcium. In wasting diseases, or when a limb has been immobilized in a plaster cast, or after paralysis, the density of the bone may change, leading to rarefaction, disuse atrophy. Deformities or other changes leading to alteration in the direction of stresses or of strains may be followed by changes in the architectural structure. All these changes are in the nature of

reflex responses to local needs, and, like other reflex responses, will fail to function properly if the reflex arc is anywhere broken. This gives the clue to the nature of the changes in the joints in disease of the central nervous system. The structure and density of the bone about the joints is determined by the character of the stimuli coming from the joints. In tabes, the arc connecting these deep centripetal impulses with the corresponding centrifugal impulses is interrupted. The changes found in the Charcot joints of tabes are such as we should predict; the bone becomes soft and rarefied and structureless; it disappears from where it should be present, and appears in the form of osteophytic outgrowths where it should not be present. Bone metabolism is going on, but neither the density nor the structure is determined by the local needs; the metabolism is "running wild." This lack of order or system in the metabolism applies also to the soft parts about the joint; the articular surfaces may disappear. The changes in syringomyelia are probably of the same general nature.

The *third type* of chronic arthritis includes not only those cases secondary to known infection in other parts of the body, but also many cases in which no infection can be discovered. The latter group of cases are put in this class, because they present the clinical characteristics which are typical of recognized secondary infectious arthritis. The pathological process in the joints may be due to the action of bacteria in the joints or to toxins absorbed from foci or infection elsewhere. In some cases it is possible that the metabolism of the joints is affected indirectly through the action of toxins on the central nervous system. No metabolism studies in this type of arthritis are on record in the literature.

The *fourth type* of chronic arthritis is seen in middle aged people. It affects one or two, or a few joints only, and is not progressive. There is no increase in the joint fluids, the joint slits are well preserved in radiograms, and there is little or no periarticular swelling. There is thickening and lipping, with ultimate ossification of the edges of the cartilage which can be felt on palpation and seen in X-ray plates.

The *fifth type* of chronic arthritis is seen in adults of any age. While only a few joints may be actively affected at any one time, the disease is progressive and usually spreads until most of the joints become involved. In the early stages there is an increase in the joint fluids, and X-ray plates show disappearance of the joint slits. In the early stages the periarticular structures are swollen and infiltrated, giving the joints a spindle shaped appearance. These swellings are soft and elastic. In the later stages, after absorption of the exudate, the joints become smaller, owing to atrophic changes in the cartilage (seen in radiograms). Later, the joints become deflected and subluxated; and muscular atrophy, bone atrophy, and atrophy of the skin and nails appears.

Table 30 shows the result of a nine-day metabolism observation made in a case of hypertrophic arthritis (Goldthwait, Painter and Osgood).

TABLE 30

METABOLISM IN HYPERTROPHIC ARTHRITIS

		P_2O_5 Grams	CaO Grams	MgO Grams	S Grams	N Grams
Urine	First day...	1.62	0.365	0.209	0.694	11.24
	Second day..	1.85	0.435	0.229	0.725	10.65
	Third day..	2.08	0.425	0.253	0.755	11.89
	Fourth day.	1.80	0.415	0.244	0.856	12.21
	Fifth day...	1.79	0.407	0.230	0.787	11.78
	Sixth day...	1.97	0.415	0.251	0.822	12.35
	Seventh day.	1.81	0.416	0.228	0.761	13.43
	Eighth day.	1.84	0.409	0.228	0.765	11.75
	Ninth day..	1.06	0.142	0.126	0.341	6.13
Total in urine.....		15.82	3.43	1.998	6.51	101.4
Feces		14.68	20.28	2.362	1.21	6.36
Total output.....		30.50	23.71	4.360	7.72	107.8
In food.....		31.66	21.24	4.778	19.25	132.9
Retained by body....		1.16	.....	0.418	11.53	25.1
Retention in per cent		4.0	.....	9.0	60.0	19.0
Lost by body.....		.....	2.47	.....	.....	.....
Loss (per cent).....		.....	11.0	.....	.....	.....

The striking features in this table are the loss of calcium and retention of magnesium and sulphur, findings similar to those in osteomalacia. A closer examination of the data shows fairly normal figures for the amount of calcium excreted through the urine, but high figures for the calcium excretion through the feces. The amount of calcium in the feces is about 96 per cent of that in the food. Normal figures are very variable, 65 to 78 per cent (Goldthwait, Painter and Osgood), but do not ordinarily reach the figures found in this case.

The amount of phosphate in the feces is about equal to that in the urine. Normal figures, though very variable, show much less phosphate in the feces than in the urine—about half as much, in our normal cases (Goldthwait, Painter and Osgood). In this case of hypertrophic arthritis, the urine contains only half as much phosphate as the food; the normal amount is much more—seventy per cent in our cases (Goldthwait, Painter and Osgood).

It has been shown that administration of calcium salts causes an increased excretion of phosphate in the feces. In accordance with the experimental data, the loss of phosphate through the feces in this case could, therefore, be considered secondary to the loss of calcium. The reverse is, of course, theoretically possible, but in view of the fact that

in this metabolism observation there is a loss of calcium, and a retention of phosphate, the loss of calcium would seem to be the primary factor.

Tables 31 to 34, inclusive, show results of metabolism observations in four cases of atrophic arthritis (Goldthwait, Painter and Osgood).

TABLE 31

METABOLISM IN ATROPHIC ARTHRITIS

		P_2O_5 Grams	CaO Grams	MgO Grams
Urine	First day	0.995	0.194	0.074
	Second day	0.894	0.217	0.078
	Third day	0.835	0.078	0.052
	Fourth day	1.098	0.219	0.070
	Fifth day	0.772	0.132	0.042
	Sixth day	1.199	0.273	0.088
	Seventh day	0.841	0.108	0.048
Total in urine		6.63	1.22	0.45
Feces		8.07	6.31	1.46
Total excreted		14.70	7.63	1.91
In food		18.20	6.64	2.07
Retained by body		3.50	.....	0.16
Retained (per cent)		19.0	.....	8.0
Lost by body		.....	0.89	.....
Loss (per cent)		.....	13.0	.....

TABLE 32

METABOLISM IN ATROPHIC ARTHRITIS

		P_2O_5 Grams	CaO Grams	MgO Grams
Urine	First day	0.863	0.214	0.0566
	Second day	0.684	0.1805	0.0596
	Third day	1.061	0.203	0.0567
	Fourth day	1.017	0.2515	0.0736
	Fifth day	0.979	0.206	0.0555
	Sixth day	0.863	0.214	0.0566
	Seventh day	0.832	0.2875	0.0486
	Eighth day	0.602	0.1565	0.0455
Total in urine		6.90	1.713	0.453
Feces		4.90	1.824	1.041
Total excreted		11.80	3.537	1.494
In food		11.10	1.876	1.50
Retained by body		.....	.....	0.0
Retained (per cent)		.....	.....	0.0
Lost from body		0.70	1.661	0.0
Loss (per cent)		6.0	90.0	0.0

TABLE 33

METABOLISM IN ATROPHIC ARTHRITIS

		P_2O_5 Grams	CaO Grams	MgO Grams	N Grams
Urine	First day	2.045	0.600	0.1602	10.10
	Second day	1.795	0.578	0.1446	11.19
	Third day	2.303	0.631	0.1367	11.37
	Fourth day	1.936	0.476	0.1087	11.46
	Fifth day	1.655	0.550	0.1170	10.08
	Sixth day	1.902	0.545	0.1276	10.88
	Seventh day	2.149	0.556	0.1616	12.25
	Eighth day	1.617	0.464	0.1362	10.47
Total in urine		15.40	6.400	1.093	87.8
Feces		9.29	11.22	1.506	7.2
Total excreted		24.69	15.62	2.60	95.0
Food		22.46	13.60	3.09	87.4
Loss		2.23	1.62	0.39	7.6
Per cent of intake lost		10.00	12.00	13.00	8.7

TABLE 34

METABOLISM IN A CASE OF ATROPHIC ARTHRITIS

		P_2O_5 Grams	CaO Grams	MgO Grams	N Grams
Urine	First day	1.436	0.419	0.0964	8.68
	Second day	0.862	0.321	0.0812	6.50
	Third day	0.704	0.327	0.0692	7.13
	Fourth day	1.056	0.483	0.0797	7.35
	Fifth day	0.599	0.210	0.0449	4.33
	Sixth day	0.987	0.365	0.0707	7.72
	Seventh day	0.923	0.329	0.0732	6.73
	Eighth day	1.043	0.305	0.0779	6.40
Total in urine		7.61	2.76	0.593	54.8
Feces		11.50	11.07	2.13	7.7
Total excreted		19.11	13.83	2.723	62.5
Food		17.34	12.46	2.525	51.6
Loss grams		1.77	1.4	0.2	10.9
Per cent of intake lost		10.0	11.0	8.0	21.0

We have, in addition, the results of one metabolism observation (Table 35) on a patient after recovery from atrophic arthritis. This is the same patient whose metabolism in the active stage of the disease is shown in Table 31.

In all four cases of atrophic arthritis there is a decided negative calcium balance. In two of the cases there is at the same time a retention of magnesium; only one of the four shows a negative magnesium balance. As in the case of hypertrophic arthritis, the negative calcium balance is to to attributed primarily to loss through the feces, the amount of calcium in the feces in these cases running from 90 to 97 per cent of that in the food.

TABLE 35

METABOLISM OF A PATIENT WHO HAD RECOVERED FROM ATROPHIC ARTHRITIS

		P_2O_5 Grams	CaO Grams	MgO Grams	N Grams
Urine	First day	2.196	0.261	0.1497	9.084
	Second day	1.997	0.164	0.1598	10.28
	Third day	1.757	0.155	0.1392	9.728
	Fourth day	1.395	0.129	0.1054	9.158
	Fifth day	1.380	0.138	012.03	8.308
	Sixth day	1.440	0.139	0.1703	8.036
	Seventh day	1.443	0.177	0.1203	8.264
	Eighth day	1.377	0.175	0.0555	8.048
Total in urine		12.99	1.34	1.021	70.90
Feces		8.33	9.81	1.66	4.83
Total output		21.32	11.15	2.68	75.73
Intake (in food)		17.02	12.49	2.50	59.04
Retained, grams		.....	1.34	.....	.....
Per cent of intake retained		.....	11.00	.....	.....
Loss		4.30	.....	0.18	16.69
Per cent of intake lost		25.00	.....	7.00	28.00

The amount of phosphate in the feces is likewise high—about the same as, or a little more than, that in the urine. Again, as in hypertrophic arthritis, the urine contains, on the average, only about half as much phosphate as the food. The loss of phosphate is in all cases less than the loss of calcium, and, as in the cases of hypertrophic arthritis, is probably secondary to the loss of calcium.

A comparison of Tables 31 and 35 is particularly instructive in this connection. These tables show the metabolism in the same patient during the active stage of atrophic arthritis (Table 31) and after recovery (Table 35). With the return to normal, as judged by the clinical condition, there is a return to the normal metabolism. Table 31 shows negative calcium balance and positive magnesium balance; Table 35 shows positive calcium balance and negative magnesium balance. Table 31 shows 95 per cent as much calcium in the feces as in the food; Table 35 shows only 78 per cent. Table 31 shows 18 per cent less phosphate in the urine than in the feces; Table 35 shows 60 per cent more phosphate in the urine than in the feces. Table 31 shows only 36 per cent as much phosphate in the urine as in the food; Table 35 shows 76 per cent.

The metabolic changes in both hypertrophic arthritis and atrophic arthritis are like those found in osteomalacia and similar bone diseases, and are probably due to the bone softening and atrophy found in the bones in these arthropathies.

According to Pemberton of Philadelphia, chronic arthritis, without distinction of clinical type, apparently, is a disease in which the body cannot metabolize the normal amount of carbohydrate and protein (Pemberton(*b*)(*c*)(*d*)(*e*)). This etiology is based on the good clinical results

which, according to Pemberton, follow administration of diets in which protein and carbohydrate are restricted in quantity, and replaced in part by fat. During the war Pemberton studied different phases of the metabolism in a number of cases of chronic rheumatism (Pemberton and Robertson, Pemberton and Tompkins, Pemberton and Foster, Pemberton and Buckman). He found no change in the basal metabolism or in the metabolism of protein, fat, or carbohydrate so far as disclosed by studies of the respiratory exchange. The urea, non-protein nitrogen, carbon dioxid combining power, calcium, fat, cholesterin, and glucose of the blood were within normal limits. He found that the blood creatin is occasionally a little high. He found, likewise, that after administration of glucose the blood sugar rises higher than it does normally after similar dosage, and returns to the starting level more slowly than in normal persons. He found no marked abnormality in renal function.

Chronic rheumatism, or, at any rate, certain forms of chronic rheumatism and gout have always been supposed to be closely related. And the belief is widespread that the chronic arthropathies are the consequence of a disturbance of the purin metabolism. But the experimental evidence, published up to now, indicates no marked deviations of purin metabolism from the normal (Ackeroyd(*b*), Mallory(*b*)).

The Pathology of Metabolism in Infancy and Early Childhood . . . . . *W. McKim Marriott*

Disturbances of the Metabolism Due to an Excessive Intake of Food—Metabolism in Infantile Diarrhea—Metabolic Disturbances Due to an Insufficient Intake of Food—Metabolism in Athreptic Infants—Disturbances Due to Insufficiency of Certain Elements in the Diet—Disturbances Due to a Deficiency in the Mineral Salts of the Diet—Disturbances of Metabolism Due to a Deficiency of the Accessory Food Factors (Vitamines)—Disturbances Due to a Diminished Capacity of Certain Organ Systems—Tetany or Spasmophilia—Metabolism in "Exudative Diathesis" (Eczema).

The Pathology of Metabolism in Infancy and Early Childhood

W. McKIM MARRIOTT

ST. LOUIS

The metabolic processes of the young are essentially the same in character as those of the adult but are relatively much more active. In the case of infants and young children a large intake of food per unit of body weight is necessary not only to supply material for growth but also to allow for a very active energy exchange. Thus an average breast fed infant ordinarily takes in food having a fuel value of approximately 100 calories per kilogram of body weight per day or about three times as much per unit of weight as an adult doing a moderate amount of work. Approximately 15 per cent of the food taken in under normal conditions is used for growth. This latter figure is based on the known average gain in weight and the caloric value of the solid material which comprises the new tissue formed.

On account of the very active metabolism during infancy, all of the organs of the body concerned with the utilization of food are constantly working at much nearer their limits of capacity than in the case of older individuals. The margin of safety is small and when any of the organs are overtaxed by excessive demands made upon them or when their functional capacity is decreased, even though only temporarily, as the result of infection or other influences, the course of metabolism may be profoundly altered.

Fortunately the young organism recovers relatively rapidly from the results of disordered metabolism and permanent damage is not so likely to occur as in the case of the adult. The overtaxing of an individual organ is not so serious when processes of growth and repair are active. Thus the capacity of the pancreas is often overtaxed in infancy, transitory glycosuria is frequent and there may be evidences of an insufficient formation of the "external" secretion, but as the pancreas ordinarily doubles in size during the first four months of life, complete recovery of function is usual. The same may be said of other organs concerned with the metabolism.

The high basal metabolism of the young individual results in the rapid

depletion of the reserve fuel depots of the body whenever the intake of food is diminished or cut off, and serious destruction of body tissue may be the ultimate result.

The demands made upon the organ systems of the infant are great even when these systems are normal, but when there is a functional deficiency in any of the organ systems the course of metabolism is necessarily abnormal.

Disturbances of the metabolism occur when there is (1) a food intake which is greater than the capacity of the body to utilize the food, or, (2) a food intake insufficient for the requirements of the body, or, (3) a diminished functional capacity of the organs or organ systems concerned with metabolism.

Disturbances of the Metabolism Due to an Excessive Intake of Food

When a complete and properly balanced food is administered to a normal infant in an amount sufficient to cover only the basal requirements, the weight of the infant remains practically constant, individual organs or portions of the body may grow at the expense of other portions but there is no increase in weight of the body as a whole. When the food intake is increased above this minimum basal requirement, the body weight increases and the rate of increase is greater the greater the intake of food but only up to a certain point. Beyond this point the weight again becomes stationary, and if the feeding of an excess of even a well-balanced food is continued the weight of the infant declines rapidly and grave symptoms make their appearance. This relationship between food intake and the weight curve is very well illustrated in the accompanying diagram of von Pirquet(*a*) (Figure 1).

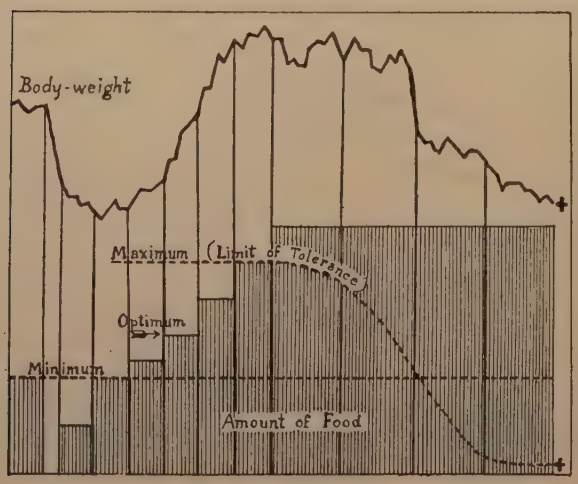


Fig. 1.

The symptoms which occur coincident with variations in the weight curve are, to a considerable extent, dependent upon the character of the food which has been administered in excess. A number of clinical types

of disturbances based upon symptom complexes have been described in great detail, but many authors have contented themselves with these descriptions and have dismissed the subject of the underlying pathology of metabolism with a few brief statements to the effect that the child's "tolerance" for food has been exceeded and that the symptoms are the result. Others state that the intermediary metabolism is deranged by an excess of food so that poisons are produced in the body but fail to state how the course of metabolism is changed or what is the nature of the hypothetical poisons.

Czerny was one of the first to attempt classification of the metabolic disturbances of infancy which result from an excessive intake of food. Under the name of "milchnährschaden" he described the clinical picture resulting from an overfeeding of milk, especially cow's milk. The same clinical picture has been described by other authors under different names such as "fat constipation," "fettnährschaden," "bilanzstörung," "chronic fat indigestion," etc. The symptoms may be of all degrees of severity. Almost any artificially fed infant may be said to show the symptoms to a greater or less degree. When the condition is well marked the infant's weight remains at a standstill or even decreases. The skin loses its normal elasticity and becomes pale and waxy in appearance. The muscular tone is poor. The infant becomes fretful and restless. The temperature fluctuates somewhat although rarely more than 2°F. except in the presence of complications. Resistance to infection is lowered so that rhinopharyngitis, otitis media, pyelitis and skin infections are liable to occur. The spitting up of small amounts of food after each feeding is frequently observed. The stools are ordinarily few in number and are putty-like in consistency, light gray in color and alkaline in reaction. The character of the stools is due to the fact that they contain a much larger percentage of calcium and magnesium soaps than do normal stools (Freund (*b*)(*c*), also Holt, Courtney and Fales(*c*)). The urine contains no albumin or casts and is essentially normal in character except for a somewhat increased ammonia coefficient. There are no gross or microscopical changes in any of the organs.

The pathogenesis of the condition is not always the same, and it would appear from metabolic studies and from clinical observation that more than one factor may be responsible. An excess of fat or protein in the food, an insufficient amount of carbohydrate or an improper mineral salt intake have all been considered as factors involved in bringing about the condition.

Inasmuch as "soap stools" are characteristically present and as clinical improvement frequently occurs coincident with alteration in the type of the stools, attention has been directed particularly to the chemical composition of these stools and to the mechanism of their formation and the metabolic changes in the body which are the result.

The stools contain relatively little free fat, negligible amounts of protein, no carbohydrate and no free organic acids. More than half of the total solid material may consist of the soaps of the higher fatty acids chiefly palmitic and stearic. Calcium soaps predominate but magnesium sodium and potassium soaps are also present. In addition there are considerable amounts of calcium phosphate. There is relatively little neutral fat (Holt, Courtney and Fales(*c*), Freund(*c*), Bahrdt). The bacteria are few in number and gram negative. The small number of bacteria is doubtless due to the fact that bacterial growth is not luxuriant in a relatively dry medium.

The conditions favoring the formation of stools of the type described are an alkaline condition in the gastro-intestinal tract, stasis in the large intestine, the presence of considerable amounts of fats in the food and sufficient mineral base, especially calcium.

An alkaline condition of the intestine may occur as the result of excessive secretion of the alkaline pancreatic juice, bile and succus entericus. Such an excessive secretion may be brought about according to Bahrdt and McLean by the presence of large amounts of fat in the small intestine especially if the fat is one which contains a considerable percentage of glycerides of the lower or volatile fatty acids. Support of this hypothesis is furnished by the fact that the character of the stools changes when the fat is decreased in amount, or fats such as vegetable oils (Freund(*b*) (*c*)), or the fat of breast milk which contains less of the lower fatty acids (Huldschinski(*a*)(*b*), Niemann(*d*)), are substituted for cow's milk fat in the food (Freund(*b*), Bahrdt).

Casein when fed in excess leads to the passage of alkaline stools. This is believed by Freund(*b*) to be due to its effect in stimulating alkaline intestinal secretions, but as purified casein has much less effect in this respect than has calcium caseinate (ordinary milk curd) it is probable that the presence of the base calcium is here the more important factor. When considerable amounts of carbohydrate are present in the gastro-intestinal tract, bacterial growth is favored and acid products are formed in considerable quantity and this may prevent the intestinal contents from becoming alkaline and thus eliminate one of the factors essential for the production of soap stools. There is some experimental evidence (Bahrdt) that calcium and magnesium salts are secreted by the large intestine and that when the contents of the colon are alkaline in reaction such sodium and potassium soaps as may be present are converted into insoluble calcium and magnesium soaps. When the intestinal contents are alkaline, there is less active peristalsis than in the presence of acid, and absorption of water is more complete on account of the longer period of time during which material remains in the intestinal tract. It also allows for the fairly complete conversion of the alkali soaps into alkali earth soaps (Bahrdt).

The passage of "soap stools" by an infant may be perfectly compatible with normal growth and development. In fact, most infants fed on cow's milk modifications pass stools which partake more or less of this character. Other infants, however, maintain a stationary weight even with abundant food intake and present the symptoms already enumerated. It is this class which is particularly considered here. One of the most obvious explanations of the failure to gain weight is that despite a sufficient food intake there is such a great loss of mineral by way of the bowel that insufficient food is absorbed. Metabolic studies by Freund(*b*) (*c*) and by Bahrdt have shown that although the stools contain considerable amounts of soaps the loss of fat in this way is small compared with the amount absorbed. The absorption of fat is usually over 90 per cent of the intake, and even in the most severe cases studied by him Bahrdt found the fat absorption to be 81.9 per cent. The loss of fat in the form of unabsorbed soap is entirely insufficient to explain the symptoms. If this loss of fat were the underlying cause of the condition the addition of a relatively small amount of fat to the diet should compensate for the loss by way of the stools, but practical experience has shown that the addition of more fat to the diet tends to aggravate the symptoms even when the total amount of fat absorbed is actually increased by this means. It is, of course, possible that altered conditions in the gastro-intestinal tract may interfere with the absorption of the essential fat soluble accessory food substance (vitamine, "fat soluble A"), but there is as yet no experimental proof that such is the case. The amount of protein and of carbohydrate lost in the stools is negligible.

The mineral metabolism shows very considerable alterations from the normal. The soap stools contain fairly large amounts of calcium and magnesium, larger in fact than can be accounted for by the combination with fatty acids in the form of soaps (Bahrdt). This excess of calcium and magnesium is combined in the form of insoluble dibasic phosphates the combination being favored by an alkaline condition in the gastro-intestinal tract. The amount of calcium and magnesium lost in this way may approximate the amount taken in with the food and in some instances exceed it, so that an actual negative balance of calcium and magnesium occurs (Birk, Rothberg, Bahrdt). In some instances, especially when large amounts of fat have been fed, there is also a negative sodium and potassium balance (Steinitz) although such a negative balance of the alkalies is not so likely to occur in these infants as in those who are suffering from diarrhea. The loss of sodium and potassium salts by the bowel is usually the result of increased secretion of the intestinal juices which have been incompletely reabsorbed. It is conceivable that the amount of base lost in this way could exceed the amount of acid excreted and thus lead to a depletion of the reserve alkali of the body, that is to say, acidosis. Steinitz has considered the high ammonia coefficient of the

urine as an indication that acidosis does in fact occur in these infants and Czerny and Keller have suggested that the low grade acidosis thus brought about is a factor in the causation of symptoms. This theory does not rest on a very firm foundation as a high ammonia coefficient is not necessarily an indication of acidosis. The more reliable methods for the detection of acidosis have failed to demonstrate that it is present. Furthermore, the symptoms are not those of acidosis and the administration of alkali fails to benefit the condition.

Whether or not acidosis occurs, the fact remains that there is a loss of mineral matter from the body and this may very well be an important factor in interfering with normal processes of growth for we know that inorganic material is an essential constituent of the body cells and fluids. If loss of mineral by the bowel were the cause of the symptoms observed one might suppose that the administration of inorganic salts in proper amounts would be the logical treatment. Some efforts have been made to treat these infants by the administration of salts by mouth but the results have not been satisfactory. It should be pointed out in this connection that even though there is a sufficient intake of mineral matter by mouth, absorption is not assured. The salt content of cow's milk is much greater than that of human but, as has been mentioned, the feeding of cow's milk results in a negative balance of certain mineral constituents.

One view of the pathogenesis of the condition under consideration is that of Benjamin, who believes that an excess of protein is the chief factor. He has shown that long continued feeding of a large amount of protein leads to the retention of a great deal of nitrogen without a corresponding gain in weight of the infant. This he interprets as evidence that overfeeding with protein leads to an abnormal composition of the body and thus interferes with the normal processes of growth and repair. Benjamin's hypothesis is in interesting contrast to the prevailing modern view that protein is relatively harmless. Holt and Levine have observed an irregular weight curve and a considerable rise in body temperature following the addition of considerable amounts of sodium caseinate to the food of infants. This they attribute to a toxic action of protein split products. Hoobler has observed serious symptoms ending in stupor following the feeding of a high protein diet to an infant. A diet such as cow's milk which contains a considerable amount of protein leads to a distinct change in the bacterial flora of the large intestine. It is a mooted question whether or not the change in the flora has an influence on metabolic processes. Porter, Morris and Meyer and Bessau present evidences for the belief that the changes in the flora are an important factor in causing a disturbance of the nutrition. Tanaka on increasing the casein of the diet three- or fourfold found a poorer retention of nitrogen than when smaller amounts of protein were fed and also poor absorption and retention of calcium and of phosphorus. Howland and Stolte, on the

other hand, found that doubling the amount of casein in the food of an infant fed on breast milk resulted in a rapid gain in weight with good retention of nitrogen, potassium, sodium, chlorin and water. They found, however, a negative calcium balance.

Against the view that an excess of protein in the diet is the only factor in producing the disturbance due to the overfeeding of milk is the fact that infants suffering from this condition do very well when fed on buttermilk enriched with carbohydrate, a mixture containing practically the same amount of protein as whole cow's milk. More recently attention has been directed to the physico-chemical characters of milk and a possible source of trouble when an excess of cow's milk is fed is seen in its high "buffer" value, that is to say, the property of the milk which permits it to unite with relatively large amounts of acid or alkali without very much change in chemical reaction. Approximately three and one-half times as much acid must be added to cow's milk in order to change its reaction to a certain degree as is necessary to change the reaction of breast milk to the same degree (Aron, Marriott(*c*)). Once cow's milk is acidified more alkali is required to again render it neutral or alkaline in reaction. This buffer action of milk is due largely to the inorganic constituents of milk, principally calcium phosphate. Marriott(*c*) has pointed out the fact that when cow's milk is fed to an infant previously accustomed to breast milk the amount of hydrochloric acid secreted by the stomach must be at least three times as great if the optimum degree of gastric acidity is to be attained. If this degree of acidity were not attained the passage of a less acid chyme into the duodenum would supply lessened stimulus to secretin formation. In addition a larger amount of alkaline intestinal secretions would be necessary to alkalinize the chyle to the optimum degree as the presence of buffer substances tends to prevent change of reaction to the alkaline side as well. We consider the digestive glands of the infant as having sufficient capacity to care for the amounts of breast milk necessary for the nutrition of the infant, but one could hardly expect the digestive system of every infant to be capable of increasing its capacity to the extent required when cow's milk is fed. If the increased secretion necessary were supplied by the gastric and intestinal glands, the mineral metabolism of the whole body would of necessity be altered as a result of the abstraction of these elements from the blood.

From what has been said, it is evident that various factors may be involved in the case of artificially fed infants who, despite an adequate intake of food, fail to gain in weight and show a characteristic train of symptoms. There is no unanimity of opinion as to just which factors are the more important and methods of treatment based on one or the other theory of pathogenesis, although successful still fail to make clear the causative factors.

When breast milk is substituted for cow's milk in amounts of equal caloric value, a gain in weight usually occurs. The character of the stools changes and the other symptoms disappear. Breast milk contains as much fat as cow's milk, but the fat is composed of a smaller proportion of glycerides of the volatile fatty acids and less of the difficultly absorbable palmitic and stearic acids. Breast milk contains less protein and has a low buffer value. The feeding of breast milk results in a change of the flora of the lower intestine. The absorption of mineral salts is better despite the fact that the salt content of breast milk is lower than that of cow's milk.

Certain modifications of cow's milk are also very effective in treating the condition. If cow's milk is so diluted that only a relatively small amount is given in the course of the day and if sugar or starch or both are added in relatively large amounts, the mixture may be fed with excellent results, as far as the symptoms are concerned. The dilution of the cow's milk lowers the fat and protein content and also the buffer value of the mixture. The relative excess of carbohydrate leads to a change in reaction of the contents of the lower intestine from alkaline to acid and as a consequence the absorption of calcium is much better (Sato, Usuki). Furthermore, the bacterial flora of the lower intestine change from proteolytic to fermentative types.

Almost equally successful as a means of treatment are mixtures of buttermilk or whole lactic acid milk with the addition of starch or sugar. Here the fat may or may not be low, the protein is not reduced but the carbohydrate is high in relation to protein, and the buffer substance is partly neutralized by lactic acid.

Every type of food which has been found to be successful in the treatment of these infants has a low buffer value and results in a change in the reaction of the contents of the lower intestine from alkaline to acid. Better retention of mineral salts occurs with each of these alterations. In the light of our present knowledge we may, therefore, state that the condition of stationary weight in infants when fed considerable amounts of cow's milk is in all probability the result of a disturbed mineral metabolism brought about by abnormal conditions in the gastro-intestinal tract.

Metabolism in Infantile Diarrhea

The effects of overfeeding are not always the same. In the metabolic disturbances just described a stationary weight with constipation and the passage of alkaline soap stools were the prominent symptoms. If overfeeding with cow's milk is continued for too long a period, and especially if excessive amounts of sugar are added to the diet, diarrhea instead of constipation is the result. The stools become acid in reaction

and the infant loses weight. The loss in weight may, in severe cases, amount to as much as 10 or 15 per cent of the total body weight in a single day. Vomiting and diarrhea are constant symptoms. In severe cases the whole appearance of the infant changes. The features become sharpened, the eyes sunken and fixed in a far-away stare or are turned upwards under the half closed lids. The skin, especially over the forehead, is likely to assume a slate gray color. Over the body it hangs in loose folds, it is dry and has lost its elasticity so that it may be picked up into ridges which remain an appreciable interval before flattening. The lips and tongue are dry and parched, the mouth is held partly open. The infant is at first irritable and restless, later the psyche becomes clouded and he lapses into a state of coma. The respirations are deeper than normal, often of the air-hunger type. The pulse is small, sometimes almost imperceptible, often rapid and irregular. The hands and feet are cold although the rectal temperature is almost invariably elevated. The urine is scanty, highly concentrated and may contain traces of albumin and a substance capable of reducing Fehling's solution. The blood is thick, does not flow easily and when centrifuged separates a relatively small amount of serum. Some degree of leucocytosis is often present.

In all infants the symptoms are not so severe. The diarrhea is less marked and the extremely toxic manifestations do not occur. The clinical picture has been described under various names such as "acute gastro-intestinal digestion", "sugar indigestion", "fermentative diarrhea" or "dyspepsia". These terms are usually applied to the milder forms of the disturbance. To the more severe forms with toxic symptoms such names as "cholera infantum", "acute gastro-intestinal intoxication", "toxicosis", "alimentary intoxication", "anhydremic intoxication" are applied.

The diarrhea of these infants may be brought about by overfeeding with any food element, but an excess of carbohydrate is by far the most frequent cause. An excess of fat may in itself lead to diarrhea but is more likely to do so when considerable amounts of sugar are given at the same time. Protein is rarely given in sufficiently large amounts to cause diarrhea. There is considerable difference of opinion as to how an excess of food brings about diarrhea. The view most generally held has been that the increased peristalsis is the result of intestinal irritation by organic acids, produced by the bacterial decomposition of carbohydrates and fat. The clinical basis for this view is the fact that the diarrheal stools are usually acid and that an excess of sugar or fat, substances which on bacterial decomposition give rise to acids, are particularly likely to lead to diarrhea. Before considering the possible bacterial decomposition products of food, it is well to point out that any sugar in sufficiently concentrated solution is capable of setting up intestinal peristalsis purely by its "salt" action and that this is probably the explanation of some of the diarrheas resulting after the administration of hypertonic sugar solu-

tions. Fats in excess are also capable of setting up peristalsis by purely mechanical effect in the same way as do the mineral oils.

In order to determine the rôle of organic acids, the products of bacterial decomposition of fats and carbohydrates, in the production of diarrhea Bahrdt and Bamberg(*a*)(*b*)(*c*) fed organic acids to animals and showed by the use of the X-ray that increased peristalsis was the result. They found that the lower members of the fatty acid series were more active in this respect than the higher acids. Thus acetic acid produced diarrhea in much smaller amounts when fed than did caproic or butyric acid. The effect of acid injected directly into the duodenum was much more marked than when fed by mouth. Talbot and Hill, Edelstein and Csonka, and Bahrdt and McLean and others have demonstrated the presence of free organic acids in diarrheal stools and have shown that the addition of sugar to the diet increased the concentration of these acids. The latter authors pointed out the fact that the concentration of acids in the stools is such that if the same concentration were present in the duodenum, peristalsis would be greatly stimulated. That such concentration occurs in the duodenum has, however, never been shown and the large intestine is barely affected by the concentration of acid present. Bahrdt and McLean found no greater concentration of acid in diarrheal stools than in the stools of normal breast fed infants although the total amount of acid excreted by the stools per day was somewhat greater in the case of the artificially fed infants with diarrhea on account of the greater volume of stools passed. Huldschinski(*a*)(*b*) found more volatile organic acids in the stomach of infants suffering from diarrhea and fed on cow's milk than in the stomachs or normal breast fed infants. The excess of free acid was, however, very small and quite insufficient in itself to be the cause of the increased peristalsis. Bahrdt and his co-workers fed dogs on milk heavily infected with various microörganisms and although diarrhea and vomiting occurred as a result it could not be shown that there was an excess of acid in the gastro-intestinal tract. They were, therefore, forced to conclude that the diarrhea was due to specific bacterial toxins. Against the theory that mere acidity of the intestinal contents is the chief cause of diarrhea, may be stated the fact that the foods most successfully used in the treatment of diarrhea are those containing a very considerable amount of free lactic acid. Furthermore, the administration of alkalies by mouth fails to check diarrhea. There is every reason why the stools should be acid when the infant is fed a considerable excess of sugar, inasmuch as the feeding of this excess of sugar results in the passage of some unchanged sugar into the lower intestine and here the ever present sugar fermenting organisms readily attack it with the production of organic acids.

There has been considerable reason for supposing that intestinal bacteria are in some way responsible for bringing about diarrhea, even if not by the overproduction of organic acids. The products of digestion

of the ordinary foodstuffs have no significant peristalsis stimulating effect in the intestine unless decomposed by bacterial action. We know from experience that diarrhea is much more common in infants fed on milk known to be contaminated and which has not been pasteurized or boiled. It is not unusual to observe the occurrence of vomiting and diarrhea in a whole group of infants fed on infected milk from a common source.

Although there is a great deal of circumstantial evidence that bacterial decomposition of food in the intestinal tract is a cause of infantile diarrhea, there is not a great deal of exact scientific proof. Studies of the bacterial flora of the stools of infants suffering from diarrhea have failed to throw a great deal of light on the subject. With the exception of bacillary dysentery, a recognized specific infectious disease, the types of microorganisms found in the stools of infants suffering from severe or even fatal diarrhea are usually not essentially different from those of the normal breast fed infant. Examinations of the bacterial flora of the upper intestine have given more definite information. Moro and Tissier have shown, on autopsy material, that the upper intestinal tract of infants suffering from severe diarrhea usually contains many organisms largely of the coli group, whereas the intestinal tracts of infants dying from causes other than diarrhea are relatively bacteria free. Bessau and Bossert have studied the bacterial flora of living infants by means of a specially constructed duodenal catheter and have demonstrated that normally the duodenum contains only a few cocci, yeasts and some gram negative bacilli (easily distinguishable from B. coli). In infants suffering from diarrhea, they found invariably an invasion of the duodenum with such organisms as B. coli and B. lactis aërogenes, organisms ordinarily present only in the lower intestine. Bahrdt, Edelstein, Hanssen and Welde found that when milk infected with certain strains of B. coli was fed to dogs in sufficient amounts to cause the passage of unkilled organisms into the duodenum a severe diarrhea resulted. Koessler and Hanke(*a*) have shown that a strain of B. coli isolated from the stools may when grown in the presence of an excess of sugar quantitatively convert the amino acid histidin, a product of the digestion of protein, into histamin (beta-imidazolethylamin), a substance which Mellanby has found capable of causing vomiting and severe diarrhea when administered by mouth. This affords an explanation of how an organism such as the B. coli, which is relatively harmless in the large intestine, where its substrat is not such as to allow of the production of toxic substances, may become harmful when transplanted to a portion of the intestine where conditions are favorable for the formation of substances capable of doing harm.

An excess of fat in the food leads to a slower emptying of the stomach and an excess of sugar affords a favorable culture medium for such bacteria as may be present in the stomach or intestines. An excess of even a

well-balanced food is of necessity slowly digested and absorbed, the unabsorbed residue may serve as a culture medium for bacteria. When the secretions of the stomach and intestines are decreased from any cause, digestion and absorption of food is slow and bacterial growth especially favored on account of lack of the antiseptic action of the secretions. Salle has shown that in hot weather the gastric juice in infants may be appreciably lessened in volume and in content of hydrochloric acid and ferments. Carlson has observed a distinct diminution of the gastric juice in the presence of fever. From these facts we have an explanation of the greater frequency of diarrhea during the summer months and its frequent occurrence in infants suffering from fever even though the fever be of parenteral origin. Diarrhea, however brought about, may, if sufficiently prolonged or severe, lead to grave disturbances of the metabolism. These disturbances are largely the result of an excessive loss of material by way of the bowel. The researches of Jundell, and of Holt, Courtney and Fales(*a*) have shown the magnitude and character of this loss. The results obtained by these various workers are essentially in accord. The diarrheal stools contain considerable amounts of nitrogenous material which is in part unabsorbed protein and in part secretion from the irritated intestinal tract. The protein loss in the stools may be two or three times as great as that in health. The loss of fat is even greater, this being mostly in the form of neutral fat and fatty acids together with small amounts of alkali or alkali earth soaps. In severe diarrhea as much as 87 per cent of the fat taken in may be lost in the stools (Jundell). Such amounts of sugar as may reach the lower intestinal tract are completely broken up by bacteria and only the end products, organic acids, appear in the stools. The amount of sugar actually absorbed is undoubtedly greatly diminished in diarrhea, but, as it is impossible to determine by analysis of the stools just how much has been destroyed by bacteria, the total absorption cannot be accurately calculated. If the infant is receiving starch considerable amounts may appear unchanged in the stools.

As to the loss of certain other organic constituents of the food such as the vitamines, bile pigments and salts we have no accurate information. It would seem practically certain that a loss of each of these substances by way of the bowel must occur during severe diarrhea.

The total mineral loss by the bowel is very great and often exceeds the intake. In this loss sodium, potassium, magnesium and chlorids are chiefly concerned (Jundell; Holt, Courtney and Fales(*a*); Steinitz). The balance of each of these elements is negative in the severe diarrheas but the loss of the chlorin ion is proportionately greater than that of either sodium or potassium (Holt, Courtney and Fales(*a*)) so that the end result is a loss of acid rather than of alkali by the bowel. Steinitz on the basis of the negative sodium and potassium balances suggested that infants with diarrhea were suffering from a "relative acidosis" as a result of the loss

of base by the bowel. He overlooked the fact that there was a greater loss of the acid elements.

The loss of calcium and of phosphoric acid is, according to all observers, hardly increased above the normal and the balance of these elements is usually positive even in very severe diarrhea. This is in marked contrast to the findings in cases of constipation with soap stools previously described. The difference is probably due to the favorable effect of an acid reaction of the contents of the lower intestine on calcium and phosphate absorption.

The loss of water in the diarrheal stools is more marked than that of any other constituent, the amount lost in this way may be as much as fifteen times as great as under normal conditions (Jundell). This loss of water is such as to threaten the water reserve of the body and, as will be seen later, is an important factor in bringing about deep-seated changes in the intermediary metabolism.

The urine of these infants is markedly diminished in volume even to the point of almost complete anuria. Such urine as is passed is highly concentrated and may contain as much or more total nitrogen in a very small volume as is contained in the entire 24-hour urine of a normal infant. The excretion of organic nitrogen by way of the urine and bowel not infrequently exceeds the nitrogen intake so that an actual negative nitrogen balance is the result. The nitrogen partition in the urine differs from that in health; the most striking changes are an excess of ammonia and of amino acid nitrogen. Albumin is generally present in moderate amounts. Modigliani, Lust(*c*), and Schloss and Worthen(*b*) have brought forward evidence to prove that the protein of the urine is, in part, food protein and which must therefore have passed unchanged through the intestinal wall.

Acetone bodies may occur in the urine in small amounts but the quantities are no greater than in the urine of normal infants during a period of underfeeding.

A reducing substance is present in the urine in almost all severe cases. Langstein and Steinitz, and Meyer(*b*) supposed this substance to be lactose which had passed unchanged through the intestinal wall into the blood and, as it could not be utilized in the body, was excreted in the urine. Schloss has, however, shown that these investigators based their conclusions on faulty chemical methods. He found the reducing substance of the urine to be invariably glucose or glucose with traces of lactose and galactose.

Mineral excretion by way of the urine differs from that during health. There is less excretion of sodium, potassium and chlorids than in the normal urine (Meyer(*b*)) and this in some measure compensates for the increased excretion by way of the bowel, but not completely so for the balance of these elements is usually negative. The excretion of calcium and of phosphorus is, if anything, slightly less than normal.

The blood of infants suffering from the severe end results of diar-

rhea is markedly altered in composition. It is concentrated by water loss (Reiss, Salge, Schloss). There is an increase in the specific gravity, the index of refraction is high and the protein content markedly increased. Thus a normal infant at 6 months of age should have a blood protein of about 6 per cent, an infant suffering from severe diarrhea may have over 9 per cent protein. The total dried residue is high, the viscosity is greater than normal. The osmotic pressure and electrical conductivity are increased which is evidence of a concentration of mineral salts as well as of colloids. The urea and total non-protein nitrogen content of the serum is high, the increase being greater than could be accounted for merely by blood concentration (Schloss). That this increase is due to a functional renal insufficiency is further shown by the high Ambard coefficient and reduced phenolphthalein excretion (Schloss). The inorganic phosphate of the serum is sometimes high (Howland and Marriott(*a*)) and there is occasionally hyperglycemia (Mogwitz). The hydrogen ion concentration of the serum is increased, that is to say, the serum is more acid than normal, the reserve alkalinity is decreased and the carbon dioxid combining capacity low. There is a low O_2 combining capacity of the hemoglobin (Howland and Marriott(*a*)). These findings are all positive evidences of the occurrence of acidosis. The acetone bodies of the blood may be moderately increased but no more than in the case of well infants undergoing partial starvation and not sufficiently increased to account for the severe degree of acidosis often present (Moore).

The cellular count and hemoglobin content of the blood obtained from the capillaries by puncture of the skin is distinctly higher (20 per cent or more) than of blood taken from the veins (Marriott(*c*)). This discrepancy is to be explained on the basis of arteriolar constriction with a damming back of corpuscles on the capillary side.

The alveolar air of infants with severe symptoms following diarrhea often has a low carbon dioxid tension. This is additional evidence of acidosis (Howland and Marriott(*a*), Schloss, Yllpo).

Functional alterations in the circulatory system occur. There is apparently incomplete diastolic filling of the heart as shown by fluoroscopic examination (Czerny(*b*)). The peripheral circulation is greatly diminished, the volume of blood passing through an extremity being often less than one-tenth of the normal amount (Utheim(*a*)). A considerable degree of fever is a frequent occurrence.

There has been much discussion as to the exact manner in which the diarrhea brings about the profound chemical and physiological variations from the normal which have been recounted above.

Finkelstein(*a*)(*b*) and Langstein and Meyer(*c*) attributed the symptoms to a poisoning of the body by sugar, especially lactose, which they believed passes through the injured intestinal wall and thus enters the circulation without first having been split into monosaccharids. They believed

that the increased permeability of the gastro-intestinal tract is brought about by irritant acids. They explained the fact that severe symptoms are not so likely to occur following diarrhea in breast fed infants, despite the high lactose content of breast milk, on the basis that the whey of breast milk tends to protect the intestinal mucosa from the harmful effects of acid. The whey of cow's milk is supposed to injure the mucosa and make it more permeable and more susceptible to the action of acids. They considered the altered mineral metabolism also as a result of lactose intoxication, on the supposition that the sugar alters the permeability of the cells of the body thus disturbing the normal salt distribution. It is also claimed by the adherents of the Finkelstein school that the whey salts of cow's milk exert an influence on the mineral metabolism. The great water loss from the body is considered secondary to salt loss. The fever is explained on the basis of a specific pyrogenic action of lactose and of mineral salts. The acidosis they do not satisfactorily explain, but Finkelstein(*a*) suggests that it may be due in part to abnormal production of acids from sugar in the intermediary metabolism and in part to a loss of alkali.

Finkelstein and his colleagues have based their theories on the observed fact that the feeding of an excess of cow's milk or of cow's milk whey to an infant suffering from diarrhea leads to an increase in all of the symptoms. That lactose enters the circulation is claimed by Langstein and Steinitz and by Meyer(*c*) but, as previously pointed out, Schloss has been unable to confirm this fact. That lactose and an excess of sodium chlorid circulating in the body is capable of doing harm is claimed by the adherents of this school on the basis of the experimental work of Finkelstein and his assistants who observed serious symptoms following the intravenous administration of lactose. Allen(*a*), Helmholz, Rosenthal (*a*) and Balcar, Sansum and Woodyat have, on the other hand, been unable to show any specific toxic effect of either lactose or sodium chlorid when injected into the circulation in any but overwhelming amounts and in concentrated solution. The discussion of the possible harmful effects of sugar and salt introduced parenterally has been chiefly concerned with whether or not fever is produced. Even if it were, it is only one symptom of severe diarrhea. There is no evidence that either the clinical picture or the characteristic changes in metabolism can be brought about by the administration of any amount of lactose or sodium chlorid.

The idea of the harmful effect of cow's milk whey is based on some experiments of L. F. Meyer(*a*) who fed infants on mixtures of cow's milk whey with the curds of breast milk and then changed the feeding to one prepared from the whey of breast milk with the curds of cow's milk. He claimed on the basis of a very limited number of experiments, that infants recovering from diarrhea, when fed on breast milk whey with cow's milk curds, progressed favorably whereas when fed on cow's milk whey with

breast milk curds there was a recurrence of all of the symptoms. Lichtenstein and Lindberg, on a large series of infants, have absolutely failed to confirm Meyer's results.

In short, the theories of Finkelstein and his colleagues are based on unconfirmed experimental work. Even granting the correctness of the observations the theory of a sugar poisoning is insufficient to explain more than a very small part of the general picture both clinical and metabolic.

There is an idea expressed in much of the current literature that toxins of one sort or another are produced in the intestinal tract during diarrhea and are absorbed into the circulation. It is quite possible that such is the case, but in the total absence of experimental evidence as to the nature of the toxins or of their mode of action speculation is fruitless.

We know that certain foods, especially easily fermentable sugars, lead to diarrhea and we know that the more severe the diarrhea the greater the loss of water and of mineral salts, as well as of organic food material, and the more marked the clinical symptoms as a result. It would seem as reasonable to assume that the loss of these substances is the cause of the metabolic disturbance as to assume the presence of a hypothetical poison.

The tremendous weight loss of these infants can only be explained by a loss of water from the body. The observed concentration of the blood is further evidence of water loss. The scanty secretion of urine is the direct result of an increase in the colloidal osmotic pressure of the blood through desiccation, for we know that when colloidal osmotic pressure exceeds the arteriolar pressure in the renal vessels secretion of urine virtually ceases (Starling). The concentration of the blood thus leads to an impairment of renal function with retention of non-protein nitrogen, urea and phosphates and a lowered phenolsulphonepthalein excretion. Failure of the kidney to excrete acid results in acidosis whether the failure is due to organic changes in the kidneys as in nephritis or due to purely functional causes as in the case of these desiccated infants. When the blood volume is diminished, from any cause, a greatly decreased volume flow results (Gesell(*a*)). A decrease in blood volume such as occurs following hemorrhage or in surgical shock leads to a compensatory constriction of the arterioles with a piling up of corpuscles of the capillary blood (Cannon, Fraser and Hooper). In the case of these infants the blood being concentrated by water loss is decreased in volume and consequently the flow is reduced and compensatory arteriolar constriction occurs. A decreased volume flow of the blood, however brought about, leads to the accumulation of acid products of metabolism in the tissues and a decreased alkali reserve of the blood (Wright and Colebrook, Gesell(*a*)). The acid produced under such conditions is, at least in part, lactic acid (Clausen (*b*)). It has been shown by Araki that in conditions accompanied by vasoconstriction glycosuria occurs, the so-called "asphyxial glycosuria." Fever is common in conditions of desiccation of the body and is due according

to Balcar, Sansum and Woodyatt, to an insufficient water reserve. Straub (*a*) has shown experimentally that desiccation of the body results in severe disturbances of the metabolism, chief among which are a negative nitrogen and mineral salt balance.

It is thus seen that there is direct experimental evidence that a water deficit in the body can account for the entire picture presented by these infants, who, following severe diarrhea, have lapsed into a toxic-like condition with grave disturbances of the metabolism and who are known to have a greatly diminished water content of the body. In the light of our present knowledge it seems more reasonable to assume that water loss is the important factor in these infants and that the harmful effect of an excess of food—especially of sugar—is due to the fact that it leads to an increase in the diarrhea and consequently to the water loss from the body.

Exactly the same clinical and metabolic picture is presented by infants who are not suffering from diarrhea but who have become desiccated by insufficient fluid intake (Marriott(*c*)), excessive vomiting, or increased loss of water due to high external temperature (Rietschel(*b*)).

When the condition of desiccation of the body or "anhydremia" has existed for any length of time such serious injury to the body cells takes place that recovery may be impossible even if the lost water is restored. If, however, in the case of diarrhea, the water loss can be checked soon enough and sufficient water and mineral matter supplied to the body, recovery may be expected.

If all food is withheld for a period and water alone given the upper intestinal tract becomes relatively bacteria free. No demands are made upon the secretory glands, there is nothing to irritate the intestine and to stimulate peristalsis, absorption of water is improved. After a period of fasting of from 12 to 24 hours a small amount of food can usually be taken without harm. The foods which are least likely to increase the diarrhea are those which contain relatively little fermentable sugar. Foods which contain very little fat are less likely to cause a continuance of the diarrhea than those from which the fat has been removed, for example, skimmed milk. Protein is well tolerated and, if anything, tends to cause a cessation of the diarrhea. The whey of cow's milk is considered harmful by Finkelstein who makes use of a preparation containing very little whey, namely, protein milk. Morse and Talbot, on the other hand, on the basis of their experience state that whey is as likely to agree as any other form of artificial food. Milk which has been artificially soured by lactic acid producing organisms is very well tolerated, this is probably due to its low "buffer" value, its freedom from bacteria, other than the harmless lactic acid organisms, and the finely divided form of its casein.

The water deficit of the tissues of these infants is great and must be made up at the earliest possible moment. In order to accomplish this it

is necessary to administer large amounts of fluid by every possible means. The administration of fluid intraperitoneally (Blackfan and Maxey) is one of the most effective means of insuring the absorption of large amounts of fluid without overtaxing the circulation. On account of the loss of mineral material from the body the injected fluid should contain not only sodium chlorid but also other salts. A modified Ringer's solution or diluted sea water is a satisfactory injection fluid.

The administration of hypertonic glucose solutions intravenously tends to promote the absorption of fluid from the gastro-intestinal tract or from the peritoneum and acts as a diuretic; furthermore, it supplies a certain amount of nourishment during the period when food by mouth is withheld.

Metabolic Disturbances Due to an Insufficient Intake of Food

Fortunately, relatively few infants suffering from diarrhea develop the severe nutritional disturbances just described. In almost all there is a temporary failure to gain or a moderate loss of weight, due most probably to the decreased amount of food material actually taken in and absorbed from the intestinal tract. With a cessation of the diarrhea and the resumption of the normal food intake the loss is often quickly regained. If, however, the diarrhea is prolonged even though not sufficiently severe to lead to the disturbances described, there may result a very considerable loss of weight and a train of well marked clinical symptoms. The infant seems to waste away, the subcutaneous fat disappears and, in extreme cases, the skin becomes paper thin, gray in color and hangs in loose folds. The ribs and facial bones are prominent, the eyes sunken. The muscular tone is poor and the infant's cry is weak. The pulse is small, often slow, and occasionally irregular. The heart sounds are feeble. The temperature tends to be below normal. There is a lowered resistance to infections of all kinds and as a result furunculosis, otitis media, bronchitis and pyelitis are of frequent occurrence. These infants are apparently always hungry and when fed amounts of food suitable for normal infants of the same age they are likely to vomit and develop very severe diarrhea. Even breast milk cannot be taken in more than small amounts. Once the condition is developed recovery is extremely slow even though the infant may later develop the capacity for considerable amounts of food as far as the gastro-intestinal tract is concerned.

The condition has been described under various names such as "marasmus", "pedatrophy", "dekomposition", "wasting disease", or "athrepsia". The last-named term, first applied by Parrot, is accurately descriptive of the condition.

Metabolism in Athreptic Infants

Although repeated attacks of diarrhea are one of the most frequent causes of athrepsia, the condition may occur independently of any gastro-intestinal disturbance. It is seen in infants who have been underfed for long periods of time or in those suffering from chronic infections. It is especially frequent in infants born prematurely and in those living under unhygienic conditions. The condition of athrepsia may be properly considered as the end result of a period of partial starvation continued for long periods of time. The term "starvation" is used in the sense of a cellular starvation and may result even when considerable amounts of food are given by mouth, as far as calories are concerned, but food which is lacking in certain essential constituents. The condition also occurs when the presence of infection increases the consumption of food beyond the intake or when infections or constitutional anomalies prevent the utilization of absorbed food.

The protein metabolism in the early stages of the condition is not greatly affected. Nitrogen absorption and retention is practically normal. Only during periods of diarrhea is there a decreased absorption of protein (Bendix, L. F. Meyer(*c*)(*d*), Freund(*a*), Courtney). Even here the loss of nitrogen is not sufficiently great to seriously threaten the nitrogen balance. When the condition of athrepsia is fully developed, however, there may be a negative nitrogen balance. L. F. Meyer(*c*)(*d*) has shown that the loss of nitrogen is chiefly by way of the urine. In a typical case Meyer found the following nitrogen balance:

Intake	Urine	Stools	Balance
5.5419 grams N	4.7158 grams N	1.2555 grams N	0.4294 gram N

Such findings are indicative of destruction of body tissue. As might be expected the mineral salt balance is also negative. This has been shown by L. F. Meyer(*a*), by Jundell and by Steinitz. The loss is chiefly of sodium, potassium and chlorin, a very considerable proportion of the loss being by way of the urine.

This negative nitrogen and mineral salt balance occurs at the time when the infant's weight has been reduced to the lowest point compatible with life. The negative nitrogen balance is quite comparable with the premortal rise of nitrogen excretion observed in starving individuals. It represents a stage where the stores of carbohydrate and fat in the body have been exhausted and the metabolic requirements are met by consumption of body proptoplasm. The excess of nitrogen and salts in the urine represents the unutilizable débris resulting from tissue destruction. The ammonia coefficient in the urine of these infants is often high. This has been explained by Pfaundler as a failure of liver function in that urea is

not formed in the normal manner so that ammonium salts appear instead of urea in the urine. It is much more likely that the high ammonia of the urine is due to the fact that there is an excessive excretion of organic acids (Utheim(*b*)); the nature and mode of origin of these acids is as yet unknown.

Fat metabolism is usually affected in the condition of athrepsia especially during periods of diarrhea. Absorption of fat is poorer than in normal infants and considerable amounts of neutral fat, soaps or free fatty acids may appear in the stools (L. F. Meyer(*d*)). The loss of fat in this way results in just so much less caloric intake and favors the further breaking down of body tissue to supply the energy demands. It has been shown by Marriott and Sisson that the amount of fat circulating in the blood of infants in the condition of athrepsia is low in those infants whose weight is stationary or who are losing, but is distinctly increased in those who are showing satisfactory weight gains. This is probably evidence of increased absorption of fat in the infants who are convalescing from the condition.

Carbohydrates fed to athreptic infants seem to be well absorbed except when given in sufficient amounts to cause diarrhea, in which condition there may be considerable amounts of lower fatty acids in the stools, these fatty acids being the result of bacterial fermentation of sugar and representing a loss of food material from the body. Sugar itself rarely occurs in the stools except in very severe diarrhea. Starch may, however, occur in considerable amounts when the infant is receiving starch-containing foods. Athreptic infants have the capacity for utilizing very large amounts of carbohydrates when introduced parenterally. The amount which can be administered without leading to glycosuria is very high per kilo of body weight as compared with normal infants or adults (Helmholz and Sauer, Porter and Dunn).

The basal energy metabolism of athreptic infants is often high as compared with those who are normal. Bahrdt and Edelstein(*c*) found the total energy exchange of an athreptic infant to be 1711 calories per square meter (Lissauer's formula), an amount about 50 per cent greater than normal. Frank and Wolf observed a basal metabolism of 123 calories per kilo (normal about 65 calories per kilo) in an athreptic infant. In this same infant the food intake represented not over 108 calories per kilo. It is very easy to see why such an infant is compelled to utilize body tissue as food. As a cause of this greatly increased metabolism Frank and Wolf suggest an overactivity of the digestive glands in response to some stimulus in the gastro-intestinal tract. They do not, however, prove the correctness of this assumption. Similar high figures for the basal metabolism were obtained by Niemann(*d*) and by Rubner and Heubner.

The condition of athrepsia which has just been considered although

it occurs often as the result of prolonged diarrhea brought about by overfeeding is essentially a condition resulting from an insufficient amount of food available for building up body tissue.

During the stage of development of athrepsia, all of the evidence points to the fact that there is a breakdown of body tissue. This destruction of body substance is not confined to the solid portions of the organism but affects the blood as well. There are a diminution in blood protein, a destruction of blood corpuscles, and a decrease in the total blood volume (Marriott(*c*), Utheim(*a*)). Diminution in blood volume has the same effect in these infants as diminution of blood volume brought about in any other manner. There is a diminished blood flow (Utheim(*a*)) at least in the peripheral portions of the body. The flow of blood through the internal organs has not been measured so that we do not know if it is decreased in amount or not. It would seem likely that a decreased flow of blood occurs throughout the body, and if this were true one would expect a lowering of the functional capacity of all parts of the body.

There is considerable evidence that the functional capacity of the body is lowered, and furthermore, when the blood volume is increased there is a return of normal function.

The treatment of the condition of athrepsia based on the known changes in metabolism is to supply a food containing all of the essentials necessary for building up body tissue and one which will at the same time have a sufficient caloric value to cover the rather high energy demands. Furthermore such food must be one which can be digested and absorbed by an infant whose gastro-intestinal tract is functionally weak.

The capacity of these infants to utilize food may be increased by methods which restore the blood volume to normal. For this reason transfusion is a valuable preliminary in any form of treatment. Unfortunately, the blood volume even when restored to normal by transfusion often fails to be maintained and for this reason repeated transfusions may be necessary. A substitute for blood which is of some value is a solution of glucose and gum acacia (Marriott(*c*)). Such a solution supplies a certain amount of food and tends to maintain blood volume.

Infants, and especially athreptic infants, are able to digest a larger amount of food if given in the form of breast milk than in any of the prepared mixtures of cow's milk. Furthermore, breast milk supplies all of the essential elements necessary for building up the body. When breast milk is not available some form of artificially soured cow's milk is the most valuable food. The infants are usually able to take a larger amount of acidified cow's milk than of sweet cow's milk. It is an advantage to these infants if a large amount of sugar can be fed, as this supplies a readily utilizable form of energy and tends to spare protein destruction. Larger amounts of dextrin and maltose may be fed than of some of the other sugars. Sugar may also be given intravenously in the form of a

10 per cent glucose solution and considerable amounts may be given intraperitoneally in the form of an isotonic glucose solution, or glucose saline mixture. Athreptic infants show a curious behavior in their reactions to food. Many of them will maintain a constant weight for quite a long period and then with no change in the food or surroundings slowly begin to gain. This period of repair seems to be a period during which some necessary change in the physiology of the body is taking place. Experiments on animals in which the condition of athrepsia was duplicated suggest that the period of repair may be a period during which the blood volume is being restored to normal (Utheim(*a*)).

Disturbances Due to Insufficiency of Certain Elements in the Diet

When an infant or older child is fed on a diet which is sufficient to supply the energy demand but which is lacking in protein and fat very characteristic symptoms and disturbances of the metabolism are likely to result.

The condition was well described by Czerny under the name of "mehlnährschaden" or "starch nutritional disturbance." As edema is one of the striking features of the condition, it is sometimes referred to as "nutritional edema" or "war edema." The condition is seen in infants who have been fed for prolonged periods on a food composed largely of cereals, or cereal gruels, or sugar with very little milk, or with merely skimmed milk added. Such poorly balanced feeding may be given on account of inability to obtain milk due to failure of the supply or to poverty of the parents. Sometimes such a diet is used to correct a diarrhea and is kept up for long periods of time for fear that a return to a normal diet would result in a recurrence of the diarrhea. Infants with hypertrophic stenosis of the pylorus are occasionally fed on thick cereal mixtures containing very little milk in order to prevent vomiting. Under war conditions, the supply of milk and other foods is often reduced so that the diet of children may be composed almost entirely of starches.

The use of proprietary infant foods by ignorant parents on the assumption that these foods, which are largely carbohydrate, are good substitutes for milk is frequently responsible for the development of the condition. The very severe types of nutritional edema with accompanying symptoms are not so frequent in this country as they are in Europe. A mild degree of the disturbance is, however, quite frequent and is seen especially in infants who have been fed for long periods of time on one of the sweetened condensed milks. Sweetened condensed milk is a food which contains a very high proportion of sugar with relatively little protein and fat and cannot be so diluted as to give an adequate amount of

protein and fat without at the same time supplying an excessive amount of carbohydrate.

In the severe form of the disturbance, as seen in infants, there is, at the outset, usually a rapid increase in weight which may be mistaken for a satisfactory normal gain. Soon, however, it is noticed that the infant is definitely edematous. The edema may be of the most extreme degree so that the skin appears like a thin membrane filled with water. The edema is not dependent upon either cardiac or renal involvement. There are no signs referable to the heart. The urine, aside from being scanty in amount, during the period of increasing edema is normal in composition.

The edema may vary from day to day and it is not infrequent to observe the loss of a large portion of the body weight within a single day's time.

Infants with this condition have very little resistance to infection. They suffer frequently from attacks of otitis media, bronchitis, furunculosis and pyelitis. They are more likely to succumb to any of the acute infectious diseases than is the normal infant. In the more advanced cases a marked hypertonicity of all the muscles of the body is a prominent feature. The outlines of the separate muscles may be seen through the skin and there may be a general rigidity of the body with opisthotonos. A chronic inflammatory process in the conjunctivæ may make its appearance (xerosis conjunctivæ), the sclera may become softened so that the contents of the eyeballs exude (keratomalacia). So far reference has been made especially to the effects of a one-sided dietary on infants because the condition is of more frequent occurrence at this time of life. Older children, except under conditions of war or extreme poverty, are rarely fed diets consisting of such great excess of carbohydrate and so little fat and protein. The condition does occur in older children, however, and has been observed repeatedly during the World War. It has also been seen in child caring institutions (Bloch). The symptoms do not differ essentially from those observed in infants.

Metabolism differs from the normal chiefly in so far as water and salts are concerned. Lederer found a high water content of the blood and Weigert(*a*) a high water content of the tissues as well. Salge found a diminished amount of chlorids in the urine and a lowered salt content of the blood plasma. Blauberg determined that there was a loss of mineral matter from the body.

There have been, in general, two theories as to the pathogenesis of the condition. (1) That it is due to an excess of carbohydrate. (2) That it is due to a deficiency of fat or protein. The more recent work on the subject would indicate very definitely that the condition is a deficiency disease. For example, Bloch observed a large number of cases in infants fed on a diet of skimmed milk. These all suffered from the

characteristic eye condition and many from marked edema. Prompt recovery occurred on the addition of whole milk and cod liver oil to the dietary without any alterations in the amount of carbohydrate given. In a group of older children fed on partially skimmed milk and on oleomargarine in place of butter the development of xerophthalmia and edema occurred. The xerophthalmia cleared quickly on adding a small amount of cod liver oil. In these cases there was sufficient fat in the diet but an insufficiency of the essential "fat soluble A." As the condition improved after this was added in the form of cod liver oil, the evidence points most strongly to the fact that deficiency of this accessory foodstuff is the important factor in bringing about the condition. Bloch believes from his observations that the occurrence of severe nutritional edema is more frequent in individuals who have been deprived of all fat than in those who receive some fat even though it may be such fat as margarine which does not contain the "fat soluble A". Harden and Zilva have reproduced the condition in a monkey by feeding a diet deficient in "fat soluble A" and in protein.

A deficiency of protein alone in the diet results in a failure to gain in weight at the normal rate. Anemia of a secondary type is likely to develop. The minimum protein requirement of infants is about one and one-half grams per kilogram of body weight per day, but the majority of infants maintain their nutrition better when as much as two and one-half or three grams of protein per kilogram of body weight per day is fed. Proteins deficient in such amino acids as trypophane, lysin and cystin are of less value from the nutritional standpoint than proteins containing amino acids in which the relative proportions approach that in body protein. Proteins which are entirely lacking in one or more of the essential amino acids have a nutritional value comparable to carbohydrate. Such incomplete proteins fail entirely to supply the body's protein demands. Lactalbumen is a protein containing all of the essential amino acids in proportions which are better suited for the nutritional requirements of the infant than has any other known protein. Casein is relatively deficient in some amino acids, notably cystin, and is consequently of less value in nutrition, that is to say, a larger amount of casein must be fed to accomplish the same nutritional result as when lactalbumen is fed (Osborne and Mendel(*f*)). An infant fed on cow's milk with its relatively high casein and low lactalbumen content, therefore, requires more protein than one fed on breast milk in which the protein is largely lactalbumen.

A deficiency of carbohydrate in the diet of an infant or young child may result in those disturbances of the metabolism that have been described previously in considering the effects of a diet containing a relative excess of protein and fat. Without a fair amount of carbohydrate there is usually a failure to gain in weight, less storage of nitrogen, or, in

other words, less building up of body protoplasm. Especially noticeable are the effects of carbohydrate deprivation on very young infants. Under normal conditions, for example, in an infant fed at the breast, carbohydrate furnishes a very large part of the energy requirement and when this element of the food is lacking fat and protein must be metabolized instead. The infant organism does not seem to be able to adapt itself to the use of such a fuel. Infants fed on insufficient carbohydrate do not thrive and may develop a moderate degree of acidosis due to the acetone bodies. If such a diet is continued any length of time, collapse and death occur. No extensive metabolic studies have been made on infants fed in this manner.

Disturbances Due to a Deficiency in the Mineral Salts of the Diet

Human milk seems to contain sufficient mineral salts for the demands of the normal infant, with the possible exception of iron. There is no evidence that a breast fed infant's nutrition may be benefited by the addition of extra mineral salts to the dietary.

Cow's milk contains three times the amount of mineral matter as does human milk, but the proportions in which the different mineral constituents occur are different. There is, in cow's milk, as compared with human milk a relative excess of calcium and phosphoric acid, a moderate excess of sodium salts and a deficiency in potassium salts. When cow's milk is diluted to the extent customary in preparing it for infant feeding, the amount of mineral salts present is still sufficient for the normal infant, as is shown by the very satisfactory results following the feeding such milk dilutions. On account of the relatively small amount of potassium salts present in cow's milk, it has been suggested that an addition of potassium salts to cow's milk dilutions might be indicated. Friedenthal was probably the first to attempt this form of modification of the mineral content of the milk. Numerous other investigators have since tried out the effects of such additions of potassium salts but the evidence is by no means conclusive that such a procedure is of benefit in the nutrition of infants. It is not surprising that this should be the case as even those infants who are fed on dilute cow's milk excrete a certain amount of potassium salts in the urine, this being fair evidence that sufficient potassium salts have been absorbed to supply the demands of the body and that what is eliminated is an unrequired excess.

The administration to infants of a diet in which the mineral salts have been reduced to a minimum (as in the treatment of eczema) results in a rapid loss of weight. If such a diet is continued for a long period collapse may occur.

Disturbances of Metabolism Due to a Deficiency of the Accessory Food Factors (Vitamines)

When the accessory food factors, or vitamines, are lacking in the diet, definite alterations in metabolism and growth result. Some of the effects of a deficiency of "fat soluble A" in the diet have already been mentioned. There is some evidence that a deficiency in the "fat soluble A" or some related fat soluble substance is a causative factor in rickets. The relationship of diet to this disease and the metabolic changes occurring are discussed elsewhere. (See article on Rickets.)

It is not positively known whether infants fed on milk modifications ever suffer from a deficiency of "water soluble B", but the results obtained by Eddy and Roper and by Daniels and Byfield following the administration of substances rich in this vitamine to infants, suggest that a milk diet may be insufficient to supply the demands of some infants for this particular accessory food factor.

Infants fed exclusively on milk which has been boiled, or those being nursed by mothers whose diet is deficient in antiscorbutic substances, may develop scurvy. (For full consideration of this disease see section on Scurvy.)

Disturbances Due to a Diminished Capacity of Certain Organ Systems

In the group of nutritional diseases due to diminished functional capacity of organ systems, one would certainly include diabetes. The metabolism in diabetes in children is not essentially different from that in adults, and does not call for special consideration in this section. It is important to realize that temporary glycosuria is not an unusual occurrence during infancy. In the great majority of instances it is of no significance.

Cretinism is an excellent example of a disturbance due to functional deficiency of an organ. This condition is considered in a special article.

Tetany or Spasmophilia[1]

There is some justification for considering infantile tetany as a disease due to a failure in function of some organ system although with our present knowledge it is not possible to state with certainty that this

[1] The term tetany is here used to include all the manifestations of the so-called spasmophilic diathesis, namely, carpopedal spasm, laryngismus stridulus, convulsions, characteristic hyperexcitability of nerves to mechanical and electrical stimuli, etc.

is the case. The removal of the parathyroid glands leads to a condition which, if not identical, is very similar to infantile tetany in practically every respect. The parathyroid glands of infants dying with tetany may show anatomical changes (Yanase). The findings of Yanase have failed of general confirmation. Bliss and also Auerbach found changes similar to those described by Yanase in the parathyroid glands of children who had no manifestations of tetany. (For literature on parathyroid glands in relation to tetany see Aschenheim.) As yet no single dietary factor has been brought into relationship to the condition of infantile tetany. The fact that the disease is more active at certain periods of the year and is more frequent in artificially fed infants than in those nursed at the breast suggests the possibility of a dietary factor. The condition is frequently but not always associated with rickets in the same individual and this suggests that there may be a common etiological factor or that the two conditions may be manifestations of a single basic disorder. As against this view may be cited the fact that many infants suffering from the most extreme degree of rickets have no evidences of tetany either latent or otherwise and that infants with active tetany may have no demonstrable signs of rickets.

In tetany there are marked and characteristic alterations in the metabolism although the underlying cause of these alterations is not clear. The most important changes are those taking place in the mineral metabolism especially that of calcium.

During active tetany there is usually observed a decreased calcium retention (Cybulski, Schabad(*a*), Orgler). During convalescence the calcium retention is improved.

Failure to retain a normal amount of calcium should result in a calcium deficit in the body, and this has been found to be the case. The calcium content of the brains of infants dying with tetany has been found to be low by most investigators. (Aschenheim.)

It is in the blood that the most marked alterations in the calcium content have been observed. Several authors have reported a low blood calcium content in individual instances. Howland and Marriott(*b*) made a study of a large number of cases of tetany and found a constant diminution in the calcium of the blood serum. In tetany with active manifestations they found the blood calcium invariably lower than in normal infants, usually less than 6 mgm. per 100 c. c. (normal 10 to 12 mgm.). In some instances the blood serum calcium was as low as 3 mgm. per 100 c. c. With improvement of the clinical condition, the blood calcium invariably increased.

The lowered calcium content of the blood is not due to the lack of calcium salts in the diet for it is often observed in the case of infants receiving large amounts of cow's milk with its high calcium content. There seems to be a failure of the body to absorb and retain such calcium as

is available. Howland and Marriott(*b*) found, however, that when large amounts of calcium salts, especially calcium chlorid, were given by mouth, an increase in the blood calcium resulted. When a sufficient amount of calcium chlorid was given to infants suffering with tetany to increase the blood calcium to an amount approximating the normal, the manifestations of tetany invariably disappeared.

The reduction in the blood calcium in tetany is so constantly observed and is so marked that it seems reasonable to assume that this lowering of blood calcium is an important factor in the causation of the condition of tetany. Additional support for this belief has been afforded by the fact that symptoms of tetany develop when the blood calcium is experimentally diminished by the injection of phosphates (Binger) or oxalates (Neurath, MacCallum and Vogel). In severe nephritis accompanied by phosphate retention in the blood and a consequent lowering of blood calcium, manifestations of tetany are not infrequently observed. In parathyroidectomized dogs the development of tetany is coincident with a fall in the blood calcium (MacCallum and Voegtlein).

The metabolism of calcium and of magnesium is so similar that one might expect a disturbance in the magnesium metabolism in tetany. There is very little data on this point. Howland and Marriott(*b*) found the magnesium content of the serum to be normal in a number of infants suffering from active tetany and this suggested that the magnesium metabolism is probably not affected.

The metabolism of the alkali metals sodium and potassium has not been as thoroughly investigated as that of calcium. There is a certain amount of indirect evidence that alterations in the metabolism of sodium and potassium may occur in infantile tetany. Aschenheim suggested that the alterations in the irritability of the nervous system observed in infantile tetany might be due to the disturbance in the relative amounts of alkali and alkali earth salts present in the tissues. He based this hypothesis on the now well known fact that nerve muscle irritability is increased by the action of sodium and potassium salts and decreased by the action of calcium and magnesium salts. According to Aschenheim's hypothesis, tetany could be caused either by a decrease in calcium and magnesium salts in the tissues or to an increase in sodium and potassium salts. Aschenheim was able to demonstrate an increase in the sodium and potassium salts in the brains of infants dying with tetany as well as a decrease in the amount of calcium salts. Zeibel, Rosenstern and Grulee noted an increase in the manifestations of tetany after the administration of sodium or potassium salts by mouth. It is a matter of clinical experience that symptoms of tetany may develop after the administration of large doses of sodium bicarbonate, especially to infants suffering from severe acidosis. As the manifestations of tetany may appear even before the acidosis has been corrected, it would seem that the ex-

cess of sodium ions present was responsible for the appearance of tetany rather than any specific action of alkali. Lust(*b*) described two cases and Raabe one in which the symptoms of tetany developed in infants coincident with the occurrence of edema, and disappeared as the edema decreased. It was suggested by them that the sodium chlorid retained in the edema fluids was responsible for the development of the symptoms of tetany. Brown and Fletcher take a similar viewpoint.

Aside from alterations in mineral metabolism, the only metabolic change of any importance which has been observed in infantile tetany is the excretion of considerable amounts of guanidin and methyl-guanidin (Paton and Findlay). These substances were found in the urines of several older children with tetany. The same substances were found in excess in the blood and urine of parathyroidectomized dogs. A possible connection between the observed changes in metabolism of guanidin and of calcium is brought out by the work of Watanabe(*d*), who has shown that injection of methyl-guanidin into animals leads to an increase in the blood phosphate content and a decrease in the blood calcium content coincident with the development of tetany.

The known alterations in the metabolism in infantile tetany furnish a basis for rational therapy. The administration of calcium salts in sufficient amounts very regularly results in the disappearance of all manifestations of the condition. Berend, reasoning from the similarity in the physiological actions of magnesium and of calcium on the nervous system, suggested the use of magnesium therapeutically in tetany. It has been found that subcutaneous injection of magnesium sulphate regularly leads to a disappearance of the symptoms of tetany. Inasmuch as calcium retention is usually better in infants fed on breast milk than in those artificially fed, it is customary to feed infants suffering from tetany on breast milk when this can be obtained. Cod liver oil when fed by mouth has been shown to lead to increased calcium retention, especially in infants whose calcium retention has been poor. For this reason cod liver oil has been widely used in the treatment of infantile tetany.

Metabolism in "Exudative Diathesis" (Eczema)

Under the name of "exudative diathesis" Czerny has described a clinical picture in infants and young children which he considers to be due to an alteration in the chemical processes of the body. He attributes the alterations in metabolism to a functional incapacity of the body to utilize food, especially fat. A congenital and constitutional factor is believed by Czerny to be the basis for the condition.

The manifestations of the exudative diathesis as described by Czerny are varied in character. One of the manifestations is a failure of the

infant to gain satisfactorily despite an abundant intake of food. Such infants as do gain in weight are flabby and pale. There is a tendency to a catarrhal condition of the skin and mucous membranes. This is manifested especially as eczema, intertrigo, rhinopharyngitis, otitis media, bronchitis and gastro-intestinal disturbances. General hyperplasia of the lymphoid tissues throughout the body occurs. There is a lessened resistance to infection.

There is considerable difference of opinion as to whether or not the exudative diathesis is in reality a definite clinical entity. The manifestations are so varied that it is quite possible a number of entirely different conditions of diverse etiology have been included. Czerny's idea seems to have received more general acceptance in Europe than in this country.

In the discussion of metabolism in the condition, it would seem best to consider only the changes occurring in those cases with manifest eczema as it is only in this group that any significant alterations in metabolism have been observed.

Steinitz and Weigert found that infants with eczema were unable to absorb fat to the same extent as normal infants. Czerny has considered this finding of importance as showing an intolerance on the part of the infant for fat. No significant changes in the nitrogen and carbohydrate metabolism have been observed, although in some cases of eczema a definite hypersensitiveness to foreign proteins has been observed (Schloss(*b*), Blackfan).

The most constant and marked features of the metabolism of eczematous infants are alterations in the water and mineral salt balance. Lust (*a*) and Lederer found at times a considerably increased water content of the blood of eczematous patients as compared with the normal infant. Most characteristic was a tendency to wide and rapidly occurring fluctuations in the water content. The variations in the amounts of water retained in the body seem to be dependent upon alterations in mineral metabolism. Thus Freund(*d*) found infants with eczema showed a much greater retention of sodium chlorid than normal infants given the same diet. The retention of sodium chlorid was coincident with rapid gain in weight due undoubtedly to simultaneous water retention. L. F. Meyer(*c*) found during periods of underfeeding of eczematous patients a much greater output of mineral salts than was observed in the case of normal infants on the same diet. This finding, together with those of Freund, suggests a very labile salt metabolism of the eczematous infant. Salts are readily retained and as readily excreted. Bruck studying a number of cases of eczema found little or no change in the mineral metabolism. It is possible that eczema is a disease of diverse etiology and that its manifestations are not always the same.

The treatment of the condition has not been any too satisfactory. In

some instances a restriction of water and of mineral salts has resulted in a prompt cure. Elimination of fat from the diet is at times equally successful as is also elimination of specific proteins to which certain of these infants are sensitive. Although there has been a large mass of clinical literature on the subject of eczema, our knowledge of the true nature of the condition and the changes that are occurring in the metabolism is most fragmentary. Regarding the other manifestations of the so-called "exudative diathesis" we know still less.

The Metabolism in Infantilism . . . . ***Francis H. McCrudden***

Introduction—Studies of the Composition of Urine—Composition of Feces—Bone Fragility—Digestion and Absorption of Gastro-Intestinal Tract—Excretion in Intestinal Infantilism—Growth and Calcium Metabolism.

The Metabolism in Infantilism

FRANCIS H. McCRUDDEN

BOSTON

Introduction

We can imagine two fundamental causes for failure of an animal to grow: (1) Absence of the capacity to grow; (2) absence of available structural material. Dwarfism occurs as the result of disease or removal of the thyroid or thymus, for example, even when the food supply is abundant. The capacity to grow, in this case, is missing. Failure to grow is not seen as the result of complete starvation; death ensues too soon for this. But partial starvation, the result of a diet rich enough in caloric value and complete enough for the bare maintenance of a young animal, but lacking certain essentials for growth may lead to dwarfism from the lack of material for growth. Both of these forms of dwarfism have been studied experimentally, and the results are fully discussed elsewhere in these volumes.

A scientific study of infantilism should, if possible, present the subject from the point of view suggested in the preceding paragraph. But the metabolism in different types of dwarfism has been so little studied that in many cases it is not yet possible to determine which of the two fundamental causes is responsible. Nearly every writer who discusses infantilism presents a classification of his own. All investigators agree that three forms of the disease are easily recognizable: cretinism, achondroplasia, and mongolianism. Besides these, every writer on the subject describes cases of infantilism which do not appear to belong to any one of these three groups; in many cases the supposed etiology is given. Thus cases of infantilism have been described as due to disease of the liver, pancreas, heart, lymphatic system, cerebral tumor; others as due to tuberculosis, chlorosis, pellagra; and still others as due to poisoning from alcohol, lead, or mercury, or to a generally poor hygienic environment.

Those who have been making scientific studies of nutrition and growth in animals have generally refrained from attempts to apply their results to the explanation of any of the recognized forms of spontaneous dwarfism occurring in man. And writers on infantilism in man have generally restricted themselves to clinical descriptions of the forms of infantilism they have observed, comparing their cases with other cases for the purpose of

merely descriptive classification, and not attempting to find any relationship between their cases and the laboratory cases of stunted growth. The first type of infantilism in which an attempt was made to study the metabolic changes with any degree of thoroughness is the so-called "Intestinal Infantilism" first described by Herter in 1908. This form of infantilism occurs in childhood, and is characterized by periods of disturbance of nutrition with loss of weight, alternating with periods of normal nutrition and gain of weight; it finally ends in a state of arrest of development in which it is almost impossible to bring about increase of weight. There are marked abdominal distention, a moderate grade of anemia; there are symptoms of rickets, and a rapid onset of physical and mental fatigue. Diarrhea, or at least looseness of the bowels, is frequent; and the stools are often fatty and foul. The appetite and thirst are excessive. The urine is frequently increased in quantity, and shows a rise in the ethereal sulphates, indican, phenol, and oxy-acids. There is a change in the intestinal flora—a reversion to the flora of the infantile type.

Herter described five cases which he had thoroughly studied and referred to five others that he had seen. Freeman described four cases. Three cases described by Schultz and others by Huebner fit into this category.

The intestinal symptoms seemed so definitely a part of the disease in this form of infantilism that metabolic changes seemed probable and were accordingly sought for by McCrudden (McCrudden(*a*), also McCrudden and Lusk).

Preliminary studies showed that the urine is low in nitrogen; the amount excreted, calculated per one square meter body surface, averages less than the starvation value (McCrudden and Fales). The feces are very bulky and contain much nitrogen. The creatinin coefficient is low (McCrudden(*a*)) and acetone is occasionally found in the urine. These, and certain other features indicating faulty nutrition and poor absorption, suggested that partial starvation might be a factor in the condition. Studies were accordingly made of the nitrogen and sulphur distribution in the urine.

Under normal conditions more than 80 per cent of the total nitrogen of the urine is present as urea nitrogen, and about the same proportion of the total sulphur as inorganic sulphates. The amount of other nitrogenous and sulphur compounds is low. In starvation and on a low protein diet, the absolute amount of urea and inorganic sulphur falls; the fraction of the total nitrogen as urea nitrogen and of the total sulphur as inorganic sulphur diminishes. The absolute amounts of nitrogen in the form of uric acid, creatinin, ammonia, and amino acids, and of sulphur in the form of ethereal sulphates and neutral sulphur remain nearly constant; the proportion of the total nitrogen and sulphur in these forms increases. Examination of the distribution of nitrogen and sulphur among the differ-

ent compounds in the urine indicates whether the protein metabolism is relatively high or low.

Tables 1 and 2 from Folin's paper on this subject (Folin(*d*)) show the nitrogen and sulphur distribution in two typical cases of high and low protein diet respectively.

TABLE 1

NITROGEN AND SULPHUR DISTRIBUTION IN THE URINE ON A HIGH PROTEIN DIET

	N	S	
Total N	14.8 — 18.2 gm.	2.4 — 3.3 gm.	Total S
Urea N	86.3 — 89.4%	82.0 — 91.0%	Inorganic S
Ammonia N	3.3 — 5.1%	5.2 — 7.6%	Ethereal S
N in other forms	6.4 — 10.8%	3.4 — 10.0%	Neutral S

TABLE 2

NITROGEN AND SULPHUR DISTRIBUTION IN THE URINE ON A LOW PROTEIN DIET

	N	S	
Total N	4.8 — 8.0 gm.	0.64 — 0.92 gm.	Total S
Urea N	62.0 — 80.4%	50.0 — 80.0%	Inorganic S
Ammonia N	4.2 — 11.7%	8.0 — 15.2%	Ethereal S
N in other forms	11.5 — 28.1%	12.0 — 37.0%	Neutral S

Tables 3 and 4 show the nitrogen and sulphur distribution in the urine in two cases of intestinal infantilism (McCrudden and Fales(*b*)).

The nitrogen in the form of urea and the sulphur in inorganic forms are very high in comparison with the nitrogen and sulphur in other forms. Such figures prove that the exogenous metabolism is high and indicate that the endogenous metabolism is not excessive. They show that the patients are probably absorbing sufficient protein for their metabolism.

Despite the normal figures for nitrogen and sulphur distribution, the other factors pointing toward some form of starvation were suggestive enough to make further studies in this direction advisable. The large amount of nitrogen in the feces compared with the urinary nitrogen are especially noticeable. Table 5 shows the figures in two cases of intestinal infantilism, and, for comparison, in one normal boy (McCrudden and Fales(*b*)).

In the case of F. S. the nitrogen in the feces is over two grams a day. In the case of F. H. the absolute amount of nitrogen is not greater than in the normal boy, but, since he was excreting only half as much per day in his urine, the relative amount is twice as great. In the case of F. S. the fecal nitrogen is 38 per cent of that in the food; in the case of F. H., 11 per cent. In the normal case it is only 7.5 per cent. The usual average

TABLE 3.—Nitrogen and Sulphur Distribution in the Urine on a Low Protein Diet (Patient F. S.)

			Day 1	Day 2	Day 3	Day 4
Nitrogen	Total N grams		5.57	5.12	4.48	5.12
	Urea	grams	4.74	4.16	3.58	4.32
	N	Per cent of total	85.2	81.4	80.0	84.4
	Ammonia	grams	0.37	0.22	0.24	0.10
	N	Per cent of total	6.5	4.3	5.4	2.3
	Amino	grams	0.38	0.42	0.31	0.30
	N	Per cent of total	6.8	8.2	6.9	5.9
	N in other forms	grams	0.08	0.32	0.35	0.40
		Per cent of total	1.5	6.1	7.7	7.4
Sulphur	Total S grams		0.391	0.320	0.288	0.344
	Ethereal	grams	0.304	0.224	0.224	0.276
	S	Per cent of total	77.8	70.8	77.8	80.3
	Inorganic	grams	0.052	0.040	0.024	0.036
	S	Per cent of total	13.3	12.5	8.3	10.5
	Neutral	grams	0.035	0.056	0.040	0.032
	S	Per cent of total	9.0	17.5	13.9	9.3

TABLE 4.—Nitrogen and Sulphur Distribution in the Urine in Infantilism (Patient F. H.)

			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Nitrogen	Total Nitrogen grams		5.68	5.44	5.27	5.62	5.87	5.56
	Urea	grams	4.96	4.80	4.64	4.94	5.10	4.94
	N	Per cent of total	87.4	88.2	88.0	88.1	87.0	88.8
	Ammonia	grams	0.264	0.228	0.260	0.256	0.212	0.152
	N	Per cent of total	4.7	4.2	4.9	4.6	3.6	2.7
	N in other forms	grams	0.15	0.41	0.37	0.42	0.55	0.47
		Per cent of total	7.9	7.6	7.1	7.3	9.4	8.5
Sulphur	Total Sulphur grams		0.432	0.412	0.392	0.428	0.452	0.424
	Inorganic	grams	0.378	0.362	0.334	0.368	0.390	0.368
	S	Per cent of total	87.6	87.9	88.3	86.2	86.5	86.9
	Ethereal	grams	0.018	0.022	0.022	0.028	0.022	0.020
	S	Per cent of total	4.2	5.4	5.6	6.5	4.9	4.7
	Neutral	grams	0.036	0.028	0.036	0.032	0.040	0.036
	S	Per cent of total	8.4	6.8	9.2	7.5	8.9	8.5

TABLE 5

NITROGEN IN THE FECES AND URINE

	Number of Days	Grams N in the Food	Grams N in the Urine	Grams N in the Feces	Average per Day	
					Urine	Feces
F. S. (intestinal infantilism).	6	35.64	16.11	13.52	2.69	2.25
F. H. (intestinal infantilism).	6	48.77	33.44	5.404	5.59	0.90
W. M. C. (normal).	6	86.10	64.97	6.488	10.83	1.08

normal is approximately 2 per cent. The urinary nitrogen in the two cases of infantilism is respectively 45 per cent and 67 per cent of that in the food. In the normal it is 91 per cent. The high fecal nitrogen is brought out strikingly by comparing the amount of nitrogen in the feces with that in the urine. In the case of F. S., it is 84 : 100; in the case of F. H., 16 : 100; and in the normal boy only 10 : 100.

From these figures it seemed possible that the foodstuffs might be incompletely digested or absorbed or too rapidly or too completely broken up in the intestine, or that products that were useless or even harmful from the standpoint of nutrition might be formed. The nitrogen distribution in the feces was, therefore, determined.

Determination of the total nitrogen, and of nitrogen in the form of soluble protein, ammonia, purin compounds, bacterial bodies, and amino acids was made (McCrudden and Fales(*c*)). Fairly definite conclusions regarding completeness of digestion, absorption of protein and protein digestion products, degree and nature of the bacterial activities in the intestine, and the presence of inflammatory conditions in the intestine may be reached from these data insofar as these points relate to the problem in hand; namely, whether or not protein is insufficiently, or too rapidly, or completely hydrolyzed, or undergoes changes giving harmless or useless derivatives, or is incompletely absorbed.

Table 6 shows the results in a case of intestinal infantilism, and Table 7, for comparison, in the case of an achondroplasiac dwarf with no intestinal symptoms.

The nitrogen distribution in intestinal infantilism is similar to that in the control. Neither the ammonia nitrogen, the bacterial nitrogen, nor the purin nitrogen is appreciably high, the findings agreeing in this respect with the normal figures for ethereal sulphates in the urine in indicating that putrefactive processes are not excessive. The figures in Table 5 give no basis for any hypothesis attributing the faulty development to improper protein digestion—incomplete hydrolysis, too rapid hydrolysis, formation of unabsorbable derivatives, or imperfect absorption of normal

TABLE 6

NITROGEN PARTITION IN THE FECES IN INTESTINAL INFANTILISM (PATIENT F. S.)

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Total Nitrogen in grams		1.576	1.572	1.444	1.344	1.184	1.064
Soluble protein Nitrogen	grams	.....	.....	.....	0.526	0.492	0.324
	Per cent of total	.....	.....	.....	39.20	41.50	30.50
Ammonia Nitrogen	grams	0.080	0.048	0.084	0.088	0.060	0.072
	Per cent of total	5.07	3.06	5.82	6.54	5.07	6.76
Purin Nitrogen	grams	0.174	0.230	.....	0.232	0.196	0.092
	Per cent of total	11.03	14.62	.....	17.30	16.50	8.65
Bacterial Nitrogen	grams	0.214	0.260	0.362	0.252	0.158	0.128
	Per cent of total	13.57	16.53	25.05	18.70	13.40	12.05
Amino Nitrogen	grams	0.053	0.070	0.055	0.1135	0.0723	0.0883
	Per cent of total	3.33	4.46	3.81	8.45	6.20	8.30

TABLE 7

NITROGEN PARTITION IN THE FECES IN ACHONDROPLASIAC DWARF (PATIENT E. B.)

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Total Nitrogen in grams		0.884	0.660	0.560	0.686	0.624	0.678
Soluble protein Nitrogen	grams	0.310	0.210	0.102	0.010	0.104	0.058
	Per cent of total	35.10	31.80	18.20	1.46	16.70	8.55
Ammonia Nitrogen	grams	0.034	0.034	0.024	0.028	0.029	0.045
	Per cent of total	3.85	5.15	4.28	4.08	4.64	6.64
Purin Nitrogen	grams	0.114	0.074	0.058	0.094	0.072	0.069
	Per cent of total	12.90	11.20	10.38	13.70	11.50	10.20
Bacterial Nitrogen	grams	0.102	0.018	0.046	0.227	0.130	0.198
	Per cent of total	11.55	2.73	8.22	33.10	20.80	29.20
Amino Nitrogen	grams	0.182	0.120	0.092	0.050	0.043	0.034
	Per cent of total	20.55	18.20	16.40	7.29	6.89	5.02

products, for example. They indicate that the nitrogen of the feces occurs in practically the same forms as in normal feces, from which we conclude that it is, presumably, of the same origin as that in normal feces, namely, chiefly excretory, and not unabsorbed material left over from the food.

In order to further test out the capacity of the gastro-intestinal tract to digest and absorb protein food, a period of high protein diet, forced up to the capacity of the patient, was maintained for two months (McCrudden and Fales(*e*)).

The nitrogen of the urine and feces before and after this period of high protein feeding is shown in Tables 8 and 9.

TABLE 8

NITROGEN IN URINE AND FECES IN INTESTINAL INFANTILISM DURING NORMAL DIET (PATIENT F. S.)

	Nitrogen in Urine Grams	Nitrogen in Feces Grams
Day 1	4.54	1.34
Day 2	2.70	3.32
Day 3	2.66	1.75
Day 4	2.50	1.48

TABLE 9

NITROGEN IN URINE AND FECES IN INTESTINAL INFANTALISM ON A HIGH PROTEIN DIET (PATIENT F. S.)

	Nitrogen in Urine Grams	Nitrogen in Feces Grams
Day 1	12.50	1.076
Day 2	15.36	1.225
Day 3	20.80	1.931
Day 4	12.88	0.797

Despite a five-fold increase of food protein in the second period, the nitrogen of the feces is not only not increased, but is actually decreased—a finding indicating that the high nitrogen of the feces on the usual lower diet cannot be due to any inadequacy in the digestion and absorption of protein. The results are in accord with the other evidence in indicating that the nitrogen in the feces is of the same origin as that in normal feces, that it is chiefly excretory and does not represent unabsorbed food residue.

Occasional occurrence of acetonuria, a low carbohydrate tolerance, and certain other features suggested the possibility of a disturbance in the formation or storage of glycogen, such that the glycogen store was constantly low and soon exhausted.

To test this possibility, the respiratory quotient after 18 hours' starvation was determined. The value for the non-protein respiratory quotient was 0.79, a figure indicating the oxidation of a mixture of fat and carbohydrate. There is, therefore, no considerable abnormality in the glycogen storing capacity.

Nothing abnormal in the digestion or absorption of fat could be found. The feces showed normal amounts of total fat, fatty acids, and soaps. Table 10 shows the distribution of fat in different forms in the feces (McCrudden and Fales(*d*)).

TABLE 10

FAT IN THE FECES IN INTESTINAL INFANTILISM

		Patient F. S.	Patient F. H.
Weight of 6 Days' Stool		231.1	117.3
Total fat	grams	34.20	18.38
	Per cent of feces	14.80	16.00
Neutral fat	grams	7.86	12.55
	Per cent of feces	3.40	10.70
Fatty acid and soap	grams	26.35	6.27
	Per cent of feces	11.40	5.35
	As normal stearic acid in c. c.	92.80	22.08

The occasional occurrence of acetonuria suggested the possibility of acidosis. But the low ammonia excretion (see Tables 3 and 4) shows that there is no acidosis.

There is nothing in the evidence to indicate any abnormality in the digestion, absorption, or intermediary metabolism of protein, fat, or carbohydrate, or in the metabolism of energy. There is nothing to indicate starvation or partial starvation in the ordinary sense of the word; the nutrition of the soft tissues appears to be normal.

One of the striking features of the disease is the bone fragility. The patient F. S. suffered bone fractures as the result of very slight trauma. Röntgenographic examination showed that the cortex of all the bones is very thin and rarefied (McCrudden(*d*)).

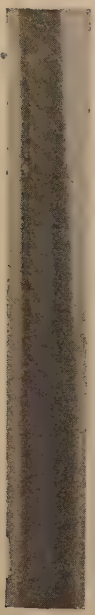
The accompanying plates show prints of *x*-ray plates of the tibia and carpal bones of one hand in the cases of F. S. and F. H., two cases of intestinal infantilism; and similar prints from dwarfs of three other types and one normal boy. The thin and rarefied cortex in the cases of infantilism can be made out even in the prints, though not of course as clearly as in the originals. The difference cannot be ascribed to differences in technique in making the röntgenograms; many plates were made at different times, and the results found were constant.

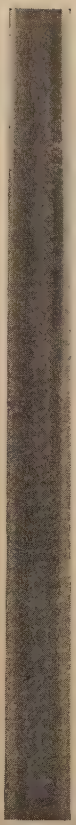
These bony changes, together with a very low calcium content of the urine, made complete balance studies of the mineral metabolism seem desirable.

Tables 11 and 12 show the results of balance studies in two cases of intestinal infantilism. For comparison, Tables 13, 14 and 15 show the results in dwarfs of three other types; and Table 16 those of a normal boy (McCrudden(*d*), McCrudden and Fales(*b*)).

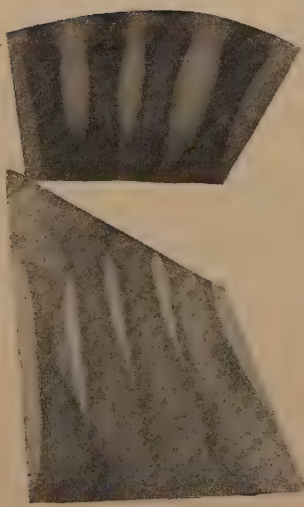
W. McL.
Normal

J. P.
Dwarf





Tibia



Metacarpal bones

Metatarsal bones

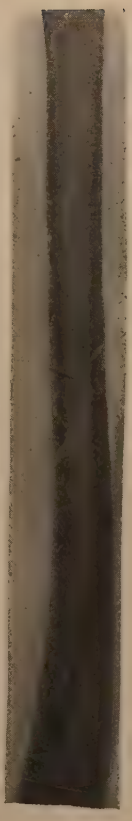
M. S.

Cretin

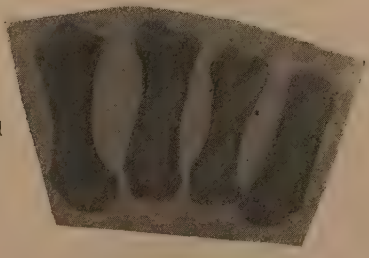
E. B.

Achondroplasia

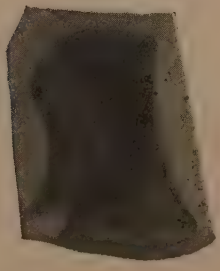
Tibia



Metacarpal bones



Metatarsal bones



F. S.

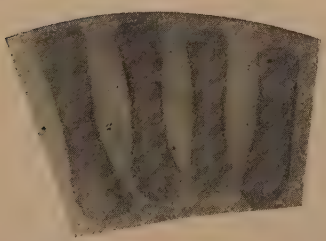
Intestinal Infantilism

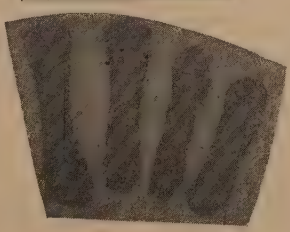
F. H.

Intestinal Infantilism

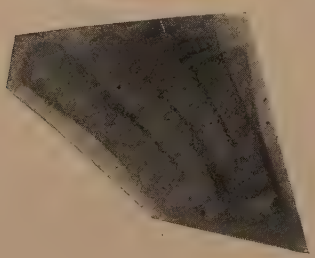
Tibia

Metacarpal bones





Metatarsal bones



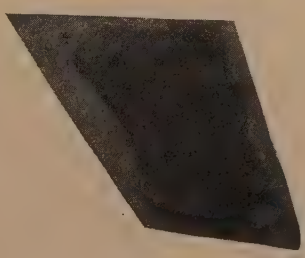


TABLE 11

METABOLISM OF PATIENT WITH INTESTINAL INFANTILISM (F. S.)

Day		Total Feces Grams	N Grams	CaO Grams	MgO Grams	P_2O_5 Grams
Urine	1	.....	2.75	0.010	0.005	0.512
	2	.....	2.76	0.016	0.070	0.520
	3	.....	3.02	0.021	0.086	0.572
	4	.....	2.75	0.012	0.074	0.497
	5	.....	2.51	0.009	0.054	0.398
	6	.....	2.32	0.040	0.111	0.211
	Total	.....	16.11	0.108	0.400	2.710
Feces	1	29.6	1.707	1.965	0.213	0.855
	2	14.32	0.868	0.750	0.009	0.767
	3	58.5	3.532	2.744	0.579	2.495
	4	40.35	2.840	1.733	0.339	1.077
	5	52.55	2.286	1.618	0.331	1.072
	6	35.75	2.288	1.451	0.229	1.073
	Total	231.1	13.52	10.26	1.700	7.34
Total intake (food)			35.64	6.35	2.43	11.91
Total outgo			29.63	10.37	2.10	10.25
Retention in grams			6.01	.....	0.33	1.66
Loss in grams			.....	4.02	.....	.....
Per cent of intake retained			16.9	.....	1.4	13.9
Per cent of intake lost			.....	63.3	.....	.....

Examination of the balances of the two patients with intestinal infantilism shows a striking loss of calcium. In the case of F. H., magnesium as well as calcium is lost. The results in the cases of intestinal infantilism were in striking contrast to those of the dwarfs of other types and those of the normal boy.

In the two other cases of intestinal infantilism, practically all the calcium excreted is in the feces. The calcium excreted in the urine is almost negligible, the amount excreted in a week being less than the normal excretion for a day. In marked contrast with the normal of twenty per cent, the amount of calcium in the urine of these two cases is only one or two per cent of the amount in the feces. In the case of F. H., there is as much calcium in the feces as in the food; in the case of F. S., there is 60 per cent more than in the food.

TABLE 12

METABOLISM OF A PATIENT WITH INTESTINAL INFANTILISM (F. H.)

	Day	Total Feces Grams	N Grams	S Grams	CaO Grams	MgO Grams
Urine	1	.....	5.68	0.432	0.050	0.061
	2	.....	5.44	0.412	0.017	0.058
	3	.....	5.27	0.392	0.014	0.063
	4	.....	5.62	0.428	0.028	0.068
	5	.....	5.87	0.452	0.018	0.073
	6	.....	5.56	0.424	0.029	0.067
	Total	.....	33.44	2.540	0.156	0.390
Feces	1	17.4	0.789	0.089	1.583	0.300
	2	21.3	0.989	0.117	1.632	0.337
	3	17.5	0.836	0.099	1.279	0.287
	4	18.7	0.899	0.102	1.265	0.308
	5	22.7	1.016	0.154	1.577	0.336
	6	19.7	0.875	0.114	1.449	0.274
	Total	117.3	5.404	0.675	8.785	1.842
Total intake (food)			48.77	4.110	8.820	1.968
Total outgo			38.84	3.216	8.941	2.231
Retention in grams			9.93	0.894	.....	.....
Loss in grams			.....	.....	0.121	0.263
Per cent of intake retained			20.3	21.8	.....	.....
Per cent of intake lost			.....	.....	1.4	1.3

The magnesium, like the calcium, is low in the urine and high in the feces. In the urine of the normal boy, the quantity of magnesium is 56 per cent of that in the feces, while in the urine of the two patients with infantilism it is only 20 per cent of that in the feces. The feces of the normal boy contains about half as much magnesium as in the food; whereas the feces of F. S. contains more than two-thirds as much, and the feces of F. H. nearly as much as the food.

The excretion of phosphates in the stools in intestinal infantilism is larger and more marked even than that of calcium and magnesium. In the feces of F. S. there is nearly three times as much phosphate as in the urine; in the normal boy the ratio is just the reverse—more than three times as much phosphate in the urine as in the feces. In the normal boy the feces contains about one-sixth as much phosphate as the food; the feces of F. S. contains more than three-fifths as much. There is nearly

TABLE 13

METABOLISM OF A DWARF (J. P.), TYPE OF LORRAINE

	Day	Total Feces Grams	N Grams	S Grams	CaO Grams	MgO Grams	P_2O_5 Grams
Urine	1	.....	5.50	0.340	0.0985	0.1180	1.285
	2	.....	6.94	0.480	0.1086	0.1030	1.354
	3	.....	7.40	0.488	0.1250	0.1130	1.433
	4	.....	7.16	0.484	0.1333	0.1100	1.164
	5	.....	6.56	0.448	0.0950	0.0945	1.212
	6	.....	7.24	0.492	0.1165	0.1095	1.284
	7	.....	6.58	0.424	0.1325	0.1190	1.315
	8	.....	6.04	0.404	0.1135	0.1114	1.208
	9	.....	6.82	0.480	0.1175	0.1015	1.284
	10	.....	6.39	0.416	0.1225	0.1165	1.004
	Total	.....	66.62	4.456	1.163	1.088	12.54
Feces	1	12.80	0.561	0.0513	0.394	0.129	0.434
	2	16.04	0.962	0.0883	0.467	0.128	0.210
	3	12.75	0.818	0.0778	0.584	0.167	0.334
	4	15.32	0.964	0.0997	0.645	0.159	0.305
	5	15.93	0.038	0.0829	0.630	0.172	0.365
	6	13.43	0.077	0.0725	0.498	0.109	0.231
	7	16.79	0.928	0.0838	0.805	0.146	0.273
	8	15.95	0.823	0.0793	0.572	0.111	0.249
	9	16.60	0.818	0.0882	0.492	0.146	0.239
	10	21.36	1.170	0.1347	0.844	0.149	0.402
	Total	157.0	8.759	0.8585	5.931	1.466	3.042
Total intake (food)			86.42	6.700	9.436	3.251	19.210
Total outgo			75.38	5.315	7.094	2.554	15.585
Retention in grams			11.04	1.385	2.342	0.707	3.625
Per cent of intake retained			12.8	20.7	24.8	21.7	18.9

twice as much phosphate in the feces of F. S. as in the feces of the normal boy, with less than half as much in the food.

The ratio of calcium to phosphate in the urine of F. S. is 4 : 100; in the normal boy 16 : 100. The ratio of calcium to magnesium in the urine is 27 : 100 in the case of F. S., 40 : 100 in the case of F. H., and about 244 : 100 in the normal boy.

TABLE 14

METABOLISM OF AN ACHONDROPLASIAC DWARF (E. B.)

	Day	Total Feces Grams	N Grams	S Grams	CaO Grams	MgO Grams	P_2O_5 Grams
Urine	1	.....	5.419	0.387	0.143	0.100	1.272
	2	.....	5.102	0.374	0.124	0.095	1.183
	3	.....	4.867	0.350	0.130	0.109	1.058
	4	.....	4.836	0.340	0.130	0.103	1.056
	5	.....	4.362	0.348	0.112	0.100	1.114
	6	.....	5.220	0.408	0.149	0.115	1.272
	7	.....	5.059	0.355	0.131	0.109	1.138
	8	.....	5.149	0.375	0.141	0.114	1.079
	Total	.....	40.01	2.937	1.06	0.845	9.172
Feces	1	18.89	0.980	0.109	0.614	0.217	0.610
	2	12.21	0.650	0.071	0.419	0.136	0.448
	3	24.91	1.407	0.152	0.765	0.306	0.842
	4	20.51	1.193	0.115	0.628	0.242	0.665
	5	14.91	0.835	0.079	0.432	0.194	0.516
	6	14.28	0.776	0.074	0.558	0.158	0.548
	7	19.27	0.995	0.111	0.802	0.212	0.636
	8	35.38	1.812	0.206	0.976	0.435	1.338
	Total	160.4	8.648	0.917	5.194	1.900	5.603
Total intake (food)			54.44	4.221	8.217	3.056	18.29
Total outgo			48.66	3.854	6.254	2.745	14.78
Retention in grams			5.78	0.367	1.963	0.311	3.51
Per cent of intake retained			10.6	8.7	23.9	10.2	19.2

Briefly summarized, the urine is almost free from calcium; the feces contains enormous amounts; there is a marked negative calcium balance.

The urine was always poor in calcium and the feces high in calcium whenever they were examined. The negative calcium balance may possibly not be continuous. The conditions may be similar to those in osteomalacia; in this condition there is a long continued loss of calcium with negative calcium balance, which gradually becomes less, until in the later stages of the severe cases, the body stubbornly retains an irreducible minimum of calcium, and calcium balance is again reached but on a lower plane.

There is further evidence for the belief that the failure to grow is associated with a disturbance of the calcium metabolism especially. As a

TABLE 15

METABOLISM OF A CRETIN DWARF (M. S.)

	Day	Total Feces Grams	N Grams	S Grams	CaO Grams	MgO Grams	P_2O_5 Grams
Urine	1	.....	6.336	0.442	0.129	0.0340	1.248
	2	.....	5.572	0.382	0.114	0.0384	1.225
	3	.....	6.475	0.515	0.120	0.0240	1.222
	4	.....	4.938	0.294	0.091	0.0297	0.897
	5	.....	5.177	0.376	0.144	0.0382	0.917
	6	.....	5.173	0.412	0.137	0.0339	0.923
	7	.....	5.014	0.364	0.116	0.0275	0.936
	8	.....	4.958	0.348	0.128	0.0338	0.954
	Total	.....	43.64	3.133	0.979	0.2595	8.322
Feces	1	6.6	0.347	0.0508	0.568	0.128	0.533
	2	8.4	0.504	0.0648	0.600	0.141	0.533
	3	6.1	0.373	0.0398	0.403	0.116	0.327
	4	7.0	0.434	0.0513	0.441	0.139	0.381
	5 } 6 }	8.1	0.457	0.0614	0.536	0.157	0.460
	7	10.4	0.539	0.0521	0.693	0.182	0.630
	8	10.65	0.589	0.0573	0.600	0.190	0.614
	Total	57.3	3.243	0.3775	3.841	1.053	3.478
Total intake (food)			57.32	3.573	6.996	1.481	16.19
Total outgo			46.89	3.511	4.820	1.313	11.80
Retention in grams			10.43	0.062	2.176	0.168	4.39
Per cent of intake retained			18.1	1.74	31.1	11.34	27.14

result of careful dietetic therapy, the general nutritive condition of F. S., which at the time of the metabolism observation reported in Table 11 was poor, became very much improved, and a second metabolism observation was made.

At the time of the first observation, the patient was a puny little child, weighing only 13.6 kilos, and so weak that he lifted his feet with difficulty in walking, had very poor muscular control, and when lying on his back was unable to lift his trunk to the sitting position by the contraction of his abdominal muscles. The stools were large and very offensive in odor, and only the very smallest quantities of food could be given without causing increased foulness.

Half a year later the change was striking. The patient had become a

TABLE 16

METABOLISM OF A NORMAL BOY (W. McC.)

	Day	Total Feces Grams	N Grams	S Grams	CaO Grams	MgO Grams	P_2O_5 Grams
Urine	1	.....	10.43	0.729	0.374	0.153	2.34
	2	.....	10.65	0.744	0.406	0.139	2.22
	3	.....	10.35	0.717	0.373	0.154	2.23
	4	.....	11.07	0.832	0.346	0.152	2.06
	5	.....	11.35	0.808	0.332	0.157	2.58
	6	.....	11.12	0.810	0.390	0.154	2.68
	Total	.....	64.97	4.640	2.223	0.909	14.11
Feces	1	22.8	1.232	0.133	1.518	0.267	0.686
	2	19.0	0.997	0.085	1.846	0.263	0.718
	3	20.9	1.165	0.115	1.784	0.288	0.768
	4	23.5	1.173	0.113	2.084	0.301	0.839
	5	15.3	0.811	0.063	1.318	0.220	0.526
	6	21.1	1.110	0.073	1.643	0.279	0.856
	Total	122.6	6.488	0.582	10.19	1.618	4.393
Total intake (food)			86.10	6.138	14.99	3.263	24.71
Total outgo			71.46	5.222	12.42	2.53	18.50
Retention in grams			14.64	0.916	2.57	0.73	6.21
Per cent of intake retained			17.0	14.9	17.1	22.4	25.0

fat, rosy, cheerful, and, apparently, healthy boy who could run, and who had excellent muscular control. His weight had increased from 13.6 to 20 kilos. But there had been almost no growth in size. There appeared to be a striking improvement in the general health and nutrition of the soft tissues. But the abnormalities referable to the skeletal system did not improve; the bones remained small and fragile, and the patient did not grow.

Table 17 shows the result of a ten-day metabolism observation at this time.

With improvement in the general nutrition, the quantities of nitrogen, phosphate, and magnesium in the urine have considerably increased and the phosphate and magnesium of the feces decreased. The urinary calcium is as low as in the earlier observation. The bulky stools with their large calcium content still persist.

These changes would seem to indicate that the failure to develop does not depend upon a general nutritional disturbance, but upon some specific

TABLE 17

METABOLISM OF PATIENT (F. S.) WITH INTESTINAL INFANTILISM AFTER PARTIAL IMPROVEMENT

	Day	Total Feces Grams	N Grams	S Grams	CaO Grams	MgO Grams	P_2O_5 Grams
Urine	1	.....	5.33	0.312	0.016	0.210	1.600
	2	.....	4.26	0.236	0.019	0.231	1.268
	3	.....	5.16	0.317	0.026	0.242	1.287
	4	.....	5.39	0.348	0.022	0.220	1.396
	5	.....	4.58	0.345	0.016	0.218	1.308
	6	.....	5.84	0.403	0.019	0.226	1.495
	7	.....	5.63	0.452	0.018	0.206	1.434
	8	.....	5.51	0.356	0.019	0.257	1.474
	9	.....	6.04	0.407	0.014	0.146	1.285
	10	.....	7.11	0.467	0.029	0.230	1.483
	Total	.....	54.85	3.643	0.198	2.186	14.03
Feces	1	60.91	3.46	0.282	1.218	0.237	0.735
	2	31.83	1.77	0.179	0.548	0.096	0.325
	3	61.91	3.62	0.323	1.245	0.225	0.691
	4	38.60	2.44	0.221	0.742	0.109	0.498
	5	44.77	2.61	0.289	0.910	0.107	0.563
	6	65.40	3.61	0.306	1.320	0.256	1.090
	7	35.97	2.10	0.151	0.653	0.100	0.436
	8	49.32	2.77	0.263	0.907	0.170	0.523
	9	48.53	2.97	0.298	0.976	0.192	0.602
	10	35.88	1.97	0.161	0.936	0.165	0.586
	Total	473.12	27.32	2.473	9.455	1.659	6.049
Total intake (food)			110.5	16.85	5.26	31.55	6.55
Total outgo			82.2	9.65	3.84	20.08	6.12
Retention in grams			28.3	7.20	1.42	11.47	0.43

disturbance referable to the skeletal system. With the improvement in general nutrition, the metabolism of those elements associated with the soft tissues rise to a higher plane. But the metabolism of calcium, an element important for bone growth, remains abnormal.

The frail and rarefied bone strongly indicates that the skeleton is growing as fast as the lime salts at the disposal of the body permit, faster in fact than it can grow and form normal bone. The available calcium seems

TABLE 18

SHOWING FREE AND COMBINED FATTY ACIDS, PHOSPHATE, CALCIUM, AND MAGNESIUM IN THE STOOLS

		Intestinal Infantilism		Normal Boy	Other Dwarfs	
		F. S.	F. H.	W. McC.	J. P.	E. B.
		6 Days	6 Days	6 Days	10 Days	8 Days
Wt. of stool (gm.)		231.1	117.3	122.6	156.9	160.4
CaO "		10.26	8.79	10.19	5.93	5.19
MgO "		1.700	1.841	1.618	1.466	1.900
P "		7.34	8.14	4.39	3.04	5.60
Total	Per cent	14.80	16.00	23.20	11.66	9.81
Fat	Grams	34.20	18.38	28.45	18.30	15.75
Neutral	Per cent	3.40	10.70	5.80	8.30	7.29
Fat	Grams	7.86	12.55	7.11	13.02	11.69
Fatty Acid and Soap	Per cent	11.40	5.35	17.30	3.36	2.52
	Grams	26.35	6.27	21.20	5.26	4.04
	Calc. as c.c. norm. stearic acid	92.80	22.08	74.60	18.52	14.22
Volatile fatty acid calc. as c.c. norm. acid		9.54	6.69	10.57	11.76	14.90
Fatty acid + volatile acid		102.34	28.77	85.17	30.28	29.12
Phosphate combined with magnesium.		2.99	3.24	2.84	2.58	3.34
Phosphate left to combine with Ca...		4.35	4.90	1.55	0.46	2.26
CaO combined as phosphate		3.44	3.86	1.22	0.36	1.78
CaO not combined with P_2O_5	Grams	6.82	4.93	8.97	5.57	3.41
	Calc. as c.c. norm. CaO	243.6	176.1	320.4	198.9	121.7
CaO not combined with phosphate or with fatty or volatile acids	Grams	3.95	4.13	6.59	4.72	2.59
	Calc. as c.c. norm. CaO	141.3	147.3	235.2	168.6	92.6

to be spread out, as it were, to occupy as much space as possible. The rate of growth of the body as a whole is, of course, determined by the rate of growth of the skeleton.

Blood was not obtained for analysis, but the low urinary calcium, in the absence of nephritis, indicates a probable low blood calcium. Stheeman and Arntzenius have recently found the blood low in calcium in this condition. The high calcium content of the feces shows what is becoming of this element.

Calcium is ordinarily excreted in the intestine combined chiefly as calcium phosphate and calcium soap. In an attempt to find if the high calcium content of the feces was secondary to abnormally high phosphate or fatty acid, quantitative analyses of the feces were made for calcium, magnesium, phosphate, total fat, neutral fat and fatty acid, and the results compared with those in other children (McCrudden and Fales(*d*)). Table 18 shows the results.

There is nothing in the figures to account for the great loss of calcium in the feces in intestinal infantilism.

From the standpoint of metabolism we can, then, divide cases of infantilism into two groups: (1) Cases in which the failure to grow depends upon a lack of available material for growth; and (2) cases in which failure to grow is due to the absence of the growing power. Cases of intestinal infantilism belong in the first group; cretins, and achondroplasiac dwarfs belong in the second group.

Pathological Metabolism in Pregnancy . . . . ***Harold Bailey***

Historical—Examination of the Urine by Modern Methods—The Urine in Experimental Liver Necrosis—Further Studies of the Urine in Toxemia—Examination of the Blood by Modern Methods—Nitrogen of the Blood—Changes of the Urea Nitrogen in the Blood—Increase in the Creatinin Nitrogen in the Blood—Increase in the Uric Acid Nitrogen in the Blood—Other Evidences of Disturbed Metabolism—Summary.

Pathological Metabolism in Pregnancy

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NEW YORK

There are changes in the maternal metabolism in normal pregnancy evidenced by the retention of nitrogen for the development of the fetus (Hoffström, Murlin and Bailey(*b*), Landsberg) and by marked gain in the mother's weight due to the storage of fat and the growth of the uterus and breasts. Moreover the maternal organs are required to detoxicate and excrete certain metabolic products arising from the fetus. These physiological changes place an extra burden upon the entire system but chiefly upon the liver and kidneys, and if these organs have but little reserve power, the borderline of the pathological condition is approached.

It is possible that the liver suffers damage in the earlier part of pregnancy by the absorption into the general circulation of toxins of an enzyme or ferment nature, derived from the action of certain cells of the ovum—the syncytium (Weichardt). An analogous condition of much milder grade and shorter duration is believed by some to exist in the non-pregnant state, in certain women, at the time of menstruation when the ovary activates ferments which produce changes in the endometrium (Keiffer).

It has been claimed by a number of observers that there is a specific liver of pregnancy with a definite pathology which is shown by a mild degree of fatty degeneration of the cells about the center of the lobules and leading to a lessened glycogenic function (Roughton, Hofbauer, Ewing). That a similar condition exists in the kidney was established by von Leyden (Leyden) and is now generally accepted. Here again, the lesion is that of a slight degree of fatty degeneration of the cells of the tubules and not infrequently accompanied by an albuminuria.

These changes in the liver and kidney occurring not uncommonly in normal pregnancy may be looked upon as the precursors of degeneration of a severe grade present in the conditions of pernicious vomiting, acute yellow atrophy and eclampsia.

Historical

Following the demonstration by Lever in 1843 of an albuminuria in 9 of 10 cases of eclampsia and the further discovery that of 50 women at

term not one had albumin unless they also showed symptoms of intoxication, there was acceptance of the idea that the convulsions were due to disease of the kidneys. The theory had already been promulgated that in these damaged states of the kidney there was an accumulation of urea in the blood and to express this condition, the term uremia was first used in 1853 (Schottin).

There were some, however, who failed to accept this explanation as fully answering all the demands of the case for, as Meigs at once pointed out, there are many cases of eclampsia that do not have an albuminuria and, on the other hand, the true cases of Bright's disease seldom have the convulsions. In support of this statement he quoted Bright's(*a*) first report where in 25 deaths but 2 patients had convulsions, and the later report describing 35 cases with convulsions in only 3. Gourbeyre in 1856 collected 164 cases of toxemia of pregnancy. Five cases had convulsions but with no albumin in the urine. Of the remainder all had albumin and 95 developed convulsions. Meigs fell back upon the explanation, now known as the Traube-Rosenstein theory, of a hyperemia of the brain as an important factor in the etiology.

The involvement of the liver in both acute yellow atrophy and eclampsia and the connection between these diseases was first noticed by Von Frerichs(*f*) in 1860. In 1879 Duncan called attention to the probable relationship between hypermesis gravidarum and acute yellow atrophy. During the next ten years, the changes in the liver were thoroughly studied from an anatomical standpoint and thus the way was cleared for the investigation of the disease as one involving the general metabolism.

Pilliet(*a*)(*b*) in 1888 and in 1890 described the liver pathology in eclampsia. In the latter paper he reported the autopsies of 22 cases with changes in the liver in all and claimed that the degeneration in this organ formed an important picture of the disease. Jürgens not only described the changes in the liver cells but also made note of the fat emboli in the liver and the general blood stream. Von Klebs found emboli in the brain, liver and kidneys, and finally the pathology of the disease became firmly established by Schmorl's(*a*) monograph in 1893. In 17 cases studied he found constant changes in the liver cells with hemorrhagic areas and periportal necrotic foci. In five of the cases he found placental cell thrombosis in the lungs. In a more recent study the same author found the liver degenerated in 71 of 73 cases of eclampsia and all the cases showed kidney involvement.

At the time when it was recognized that the liver changes were a part of the pathological picture of eclampsia, physiologists were attempting by experiment to ascertain the functions of this organ and to note the variations in disease. In 1886 Minkowski(*b*) studied the nitrogenous metabolism in geese following the extirpation of their livers. In fowls the nitrogen excretion in the urine is chiefly in the form of uric acid. Liver extir-

pation in some cases led to a marked increase of the ammonia with a corresponding decrease in the uric acid. In others the ammonia was but slightly increased. However, upon feeding amino-acids there was always a decided increase in the ammonia, even to 70 per cent of the total nitrogen. A large amount of lactic acid was also present in the urine. From these experiments it became apparent that in geese a liver function is the synthesis of ammonia to uric acid. In the absence of this organ the amino-acids could be broken down to ammonia, but further changes occurred only to a slight extent, as this particular liver function was taken up by other parts of the organism.

Hahn, Massen, Nencki and Pawlow were able to sidetrack the liver in dogs by producing an Eck fistula, whereby the inferior vena cava is connected with the portal vein. The animals showed marked toxic symptoms which resembled those of uremia. Some of the dogs survived and on being fed meat, again had all the symptoms of intoxication which was so severe that in many instances it proved fatal. The urinary nitrogen in these cases was low in urea and the ammonia was increased to 10-20 per cent. There was also an increased production of lactic acid and ammonium carbamate was present in the blood although there was no reduction of the carbon dioxid. On autopsy the livers were found to have marked fatty degeneration and atrophy. The authors concluded that under the conditions of these experiments, there was a defect in the formation of urea from ammonia and an intoxication by ammonium carbamate or by other precursors of urea; and that there was indication that urea formation goes on to some extent in tissues and organs other than the liver.

This work was the beginning of many studies of the nitrogenous metabolism in diseases of the liver and in 1895 the entire field was thoroughly reviewed by Minkowski(*c*). He collected the reports of the ammonia excretion in a number of cases of liver degeneration and found that the percentage increase was not great in many instances. Engelein in 2 cases of phosphorus poisoning found 10.6 per cent and 11.2 per cent ammonia in the urine. Von Noorden(*c*) in 2 cases of liver degeneration found 14.2 per cent and 18.1 per cent ammonia with 75.4 per cent and 71.0 per cent urea nitrogen. Munzer with 3 cases was able to show only 6.9 per cent ammonia with 91.8 per cent urea in one case, but the second had 17.3 per cent ammonia with 52.4 per cent urea and the third with alkaline urine had 36.7 per cent ammonia with 52.9 per cent urea. Richter(*b*) in a case of acute yellow atrophy found a 10 and 16 per cent ammonia excretion with 61 per cent and 72 per cent urea. These figures are important for they serve for comparison with more recent work that will be mentioned later.

Bouchard(*b*) in 1887 suggested that eclampsia was an autointoxication due to the failure of proper excretion by the kidneys of the nitrogenous products and hence their retention in the blood. Massen varied this

theory by suggesting that impaired liver function with imperfect oxidation led to the circulation in the blood of intermediate products of protein synthesis. Rivière attempted to prove that the injection of the urine of eclamptics was less fatal to animals than normal urine. He did not take into account the factor of bacterial decomposition and some 13 years later Forchheimer and Stewart showed the fallacy of drawing conclusions from such a procedure. However, although now controverted, these experiments made a definite impression on the development of the study of the disease.

The first practical test of aid in determining the onset of eclampsia was made by E. P. Davis who in 1894 reported 564 urea determinations in 84 cases of pregnancy. He found the average excretion of urea (plus ammonia) before labor was 1.4 per cent and afterward 1.9 per cent, but at the onset of convulsions it was as low as 0.5 per cent. Helouin called attention to the relationship of the urea to the total nitrogen and advised that use be made of this fact as an aid to diagnosis.

The first attempt to determine the increase in the ammonia as well as the lowering of the urea as an additional aid to the study of the metabolic disturbances was made by Whitney and Clapp in 1903. The nitrogenous substances were divided into two groups according to whether or not they were precipitated by phosphotungstic acid. Depending upon the liberation of ammonia on heating with sulphuric acid, these precipitated substances were again separated into loosely or firmly combined classes. The urines of three normal non-pregnant women were examined and then four cases of pregnancy, before and after delivery. Finally there was one case of toxemia of pregnancy and several cases of eclampsia. In the latter, there was a diminution of the urea and an increased amount of nitrogen precipitated by phosphotungstic acid and readily decomposed into ammonia. They suggested that these loosely combined nitrogens in the precipitate were partly composed of ammonia and partly of some as yet undetermined antecedent of urea.

This work was soon followed by Folin's(*b*) development of methods that permitted of an accurate separation of the nitrogen fractions.

In 1891, St. Blaise(*a*) expressed the opinion that the eclamptic attack was due to a hepatotoxemia and seven years later stated his belief that the three chief forms of pregnancy toxemias were of the same nature and due to the insufficiency of the liver, not only as regards its inability to synthetize the nitrogenous bodies to urea, but also as to its glycogenic and bile functions. Stone, in 1903, made note of the findings of leucin and tyrosin crystals in the urine of a patient who died of acute yellow atrophy and called attention to the probability of finding a high ammonia excretion in the urine of such cases. Ewing also became committed to the view that pernicious vomiting, acute yellow atrophy and eclampsia are one and the same disease; and that they have a single fundamental basis in

the metabolic disturbances which are due to the degeneration of the liver cells with resulting failure of oxidation or deamination of the protein molecule. He pointed out, however, that they could not be considered identical in all respects and that eclampsia with its more striking clinical symptom, the convulsion, might have an added factor to the disturbance of metabolism. If there is a single causative element in eclampsia he believed it to be the nephritis rather than a toxin from the fetus, placenta or uterus.

Examination of the Urine by Modern Methods

Williams in 1905 was the first to determine the ammonia in the urine and he found that in pernicious vomiting it was high, in one case as high as 40 per cent of the total nitrogen. At that time he stated his belief that an increase above 10 per cent was an evidence of greatly disturbed metabolism and an indication to empty the uterus. In the eclamptic cases the ammonia was variable but there was a marked reduction of the total nitrogen and the urea, with an increase of the amino-acids.

Edgar reported the nitrogen partitions in a case of early vomiting toxemia that late in her pregnancy developed convulsions.

Ewing and Wolf(*b*) made a most elaborate study of the divided nitrogen in all forms of pregnancy toxemias. In the pernicious vomiting cases and in four cases of acute yellow atrophy they found a marked increase of ammonia with a lowering of urea. In many instances they determined the creatinin and uric acid nitrogen but in others these fractions together with the amino-acids, purin and any other undetermined nitrogen were grouped into a class termed "undetermined" or "rest" nitrogen. They found this fraction high in most of the toxemic cases and came to the conclusion that there was a defect in the intermediary nitrogenous metabolism, resulting in a failure to split off the amino group in the synthesis of the protein molecule. This condition they termed deficient deamination. It is interesting to examine their results, especially in the acute yellow atrophy cases for here we have for comparison a number of instances of the relationship between urea and ammonia as noted on page 837 of this article. The four cases died and extensive liver autolysis and necrosis was noted in three in which autopsies were obtained.

Excluding Case 31, where the total nitrogen excretion is not known, these figures show the highest ammonia-urea relationship as 17.4 to 67.8, whereas in the figures quoted by Minkowski there were those of a case of Munzer's with the ratio of 17.3 per cent ammonia to 52.4 per cent urea.

In two fatal cases of eclampsia, one revealing at autopsy early thrombosis and moderate autolysis of the liver, the figures may be considered as

TABLE I

NITROGEN PARTITION OF THE URINE. ACUTE YELLOW ATROPHY. (From Ewing and Wolf)

Case No.	Date, 1905	Total N Gm.	Urea Ammonia %	Urea %	Ammonia %	Undet. N %
30	7/31 8/2	10.9 7.7	62.56 85.2	58.09 67.8	4.47 17.4	18.9 12.9
31	4/17	.26%	41.6	25.8	15.8	21.9
32	6/15 6/16	7.24 .94%	73.12 73.4	63.8 62.9	9.32 10.5	12.53
33	5/10	7.22	89.1	79.1	10.0	10.16

In cases Nos. 30, 31 and 33 autopsies showed that considerable autolysis or necrosis existed. Note the reduction in the urea and the moderate rise in the ammonia and undetermined nitrogen.

typical of the entire group. These figures resemble those of the yellow atrophy cases but in addition they have the creatinin and uric acid determinations and show how the separation of these fractions may reduce the so-called undetermined nitrogen. The figures will be given from two cases of pernicious vomiting. Case 7, Table II, is typical of the nitrogen partition in this disease and such figures are substantiated by others, as will be brought out later. Case 12, although fatal, never showed any increase in the ammonia fraction.

According to the clinical history of the last case (No. 12) the patient was unable to eat and apparently the nitrogen in the urine was entirely the result of the endogenous metabolism. The total nitrogen is exceedingly low and in comparison the undetermined nitrogen is high and, as a matter of fact, nearly as high as any of their figures in the toxemic cases. It would seem that the contention of defective deamination would hold good in this case as in the others; however, apparently from the fact that the ammonia is low throughout, they offer two possible explanations for the results. One is that the disease arises from some other source than a disturbance in metabolism, which may be a secondary feature, and the other, that the initial process of defective deamination was successfully met by the organism; but in the meantime other organs in the body had been so seriously damaged that the symptoms continued and death resulted in the absence of the original factors.

This case is exceedingly instructive and eliminates any stated ammonia percentage as a criterion to the condition of the patient. In the light of our present knowledge as regards urea formation there is the possibility that the small amount concerned in the endogenous metabolism is formed elsewhere than in the liver and it leaves for further consideration the reason for this high rest nitrogen.

Ewing and Wolf, while recognizing the significance of acidosis as a

TABLE II

NITROGEN IN URINE. ECLAMPSIA—FATAL. (From Ewing and Wolf)

Case	Date	Total N	Urea & Ammonia	Urea	Ammonia	Creatinin	Uric Acid	Undet. N
No. 28	10/8/06	1.73	0.75 72.2 %	0.64 61.8 %	0.11 10.4 %	0.08 7.5 %	0.06 5.8 %	0.25 14.5 %
No. 29	4/24/06	4.55	2.75 79.4 %	2.25 64.9 %	0.50 14.5 %	0.17 4.9 %	0.08 2.3 %	0.69 13.6 %
			TOXEMIA CHARACTERIZED CHIEFLY BY VOMITING					
No. 7	3/1/06	12.5	10.5 85.2%	8.8 71.0 %	1.78 14.2 %	0.15 1.18%	0.12 .96%	1.57 12.66%
Curettage	3 /2							
	3/ 3	8.82	7.33 82.8 %	5.98 67.5 %	1.35 15.3 %	0.16 1.9 %	0.19 2.2 %	1.5 13.1 %
	3/ 5	9.15	89.6 %	78.2 %	1.04 11.4 %	0.24 2.2 %	0.15 1.6 %	0.60 6.6 %
	Vomiting ceased; patient recovered.							
			FATAL CASE OF PERNICIOUS VOMITING					
No. 12 Black vomit	4/17/06	4.32	3.47 81.31%	3.37 79.0 %	0.10 2.31%	0.15 3.48%	0.09 2.08%	0.61 13.13%
Abortion	4/19							
	4/23	3.94	3.24 82.25%	3.20 81.25%	0.04 1.0 %	0.05 1.27%	0.016 4.1 %	0.63 16.0%
	4/25	2.81	2.22 79.04%	2.07 73.7 %	0.15 5.34%	0.06 2.1 %	0.12 4.27%	0.41 14.6 %
Active Delirium	4/26	2.85	2.20 77.17%	2.01 70.5 %	0.19 6.67%	0.05 1.75%	0.08 2.81%	0.52 18.27%
	5/2	7.64	4.33 78.27%	4.05 73.2 %	0.28 5.07%	0.3 5.42%	0.28 5.0 %	0.85 11.19%
Coma	5/12	7.45	82.46%	79.15%	0.25 3.31%	0.19 2.40%	0.05 .6 %	1.06 14.54%
Died	5/14							

Author's comment: Note the same general changes in the nitrogen excretion in the fatal eclamptic cases, Nos. 28 and 29 and the pernicious vomiting case, No. 7, as in the acute atrophy cases of Table I. In case No. 12 the figures represent the endogenous metabolism and suggest that deamination may take place outside of the liver. The undetermined nitrogen is high and may show the presence of a metabolite such as an amino body or oxyproteic acid.

factor in the rise of the ammonia, do not believe that the toxemia with the resultant symptoms have either acid intoxication or acidosis as a basis. One of them, Wolf, criticises Williams for failing to recognize that low total nitrogen with low urea and high ammonia in some of his cases may be explained in part by starvation.

Pearce and Jackson point out that the same criticism may be applied to the results of Ewing and Wolf, for their cases were presumably also unable to eat, and Underhill and Rand do not accept the defective deamination theory and attempt to explain the abnormal ammonia figures as the result of an acidosis. They detailed the report of observations on a pernicious vomiting case which was fed large amounts of glucose by rectum. While marked variations occurred in the ammonia figures following the administration of the sugar, nevertheless it did not control the condition nor lead to a permanent lowering of this fraction and finally the uterus had to be emptied.

The Urine in Experimental Liver Necrosis

About this time there were several experimental studies carried on in an attempt to ascertain the changes in the nitrogenous metabolism under various conditions of liver degeneration. Pearce and Jackson were able to produce in dogs, liver degeneration of varying degree by the injection of toxic sera. A diffuse degeneration without necrosis was produced by the injection of weak sera and resulted in a transient rise of the total nitrogen of the urine with a slight rise in the ammonia fraction. With the injection of older sera there was not only diffuse degeneration of the cells but also areas of focal necrosis and there were very considerable changes in the nitrogen excretion. The total nitrogen and the urea were increased and there was a marked rise in the undetermined nitrogen. The ammonia was variable but rose above the normal. They believe that the liver possesses a "factor of safety" evidenced by an increase of the functional activity of the unharmed cells.

Hydrazin produces a fatty degeneration of the liver cells without marked changes in other organs. It attacks first the cells about the center of the lobule and it destroys a large amount of liver tissue. However, a considerable portion of the tissue remains in a fair state of preservation. Underhill and Kleiner gave this substance to dogs and concluded that in this type of poisoning the partition of the urinary nitrogen was only slightly different from that which occurs in inanition. There was a marked rise in the total nitrogen and the various fractions with the exception of ammonia which remained about the same. The urea percentage was lower and there was an accompanying rise in the undetermined nitrogen. In both the fasting and the hydrazin poisoned dogs there was present considerable allantoin nitrogen.

Wolf and Osterberg in an investigation undertaken to throw light upon the behavior of creatin in starvation, poisoned fasting animals with phlorizin. This poison produces fatty infiltration and degeneration of the albumin of the liver cells. Waldvogel believes the process is closely

allied to autolysis. In these animals there was a marked increase in the total nitrogen, one case showing a rise from two to nine grams. While the ammonia was increased in actual amount, the percentage relationship was somewhat lower. Both the creatinin and creatin were increased and the authors concluded that the ratio of creatin excretion to total nitrogen steadily rises during the poisoning.

Perhaps chloroform poisoning presents in its pathological changes in the liver the closest resemblance to the liver of pernicious vomiting. Here again, the changes are in the cells about the center of the lobule.

Howland and Richards studied the nitrogen excretion in delayed chloroform poisoning in dogs and came to the conclusion that "it is a striking fact and worthy of especial emphasis that the distribution of nitrogen as urea, ammonia and undetermined, so closely approximated the normal." However, while the proportions remained the same, there was a decided increase in the amount of total nitrogen and the other fractions. In two of the dogs that died there was a marked increase in the creatin nitrogen but not proportional to the severity of the poisoning. They state that a rough index of the severity of the acute effects is given by the total nitrogen and sulphur figures and the changes in creatin.

In all of these types of artificial liver degeneration the animal is in a condition of starvation and the nitrogen represents the endogenous metabolism. The marked increase in the total nitrogen must be due to either a general stimulation of the protein metabolism by these poisons or to an increase in the nitrogen by autolysis of the cells in the injured liver. The disturbances in the creatin and the rise of the undetermined nitrogen would indicate that the latter condition exists.

Even though the injury to the liver is extreme these investigations suggest that the intermediary metabolic processes are carried on to a large extent by the remaining uninjured cells.

The nitrogen figures from these cases of experimental liver degeneration are comparable to those of the fatal case of pernicious vomiting in Ewing and Wolf's tables.

Further Studies of the Urine in Toxemia

Murlin and Bailey(*a*) in an effort to ascertain if there is evidence of defective deamination in pregnant women made a study of the nitrogen partitions of 100 urines. The amino-acid nitrogen was determined by the formal titration method or by the new method of Benedict and Murlin and the purin nitrogen was also separated, leaving for the undetermined fraction only polypeptid bodies or oxyproteic acids. The average of 33 normal urines showed urea of 77.7 per cent, ammonia of 6.7

TABLE III

POSTPARTUM ECLAMPSIA (CASE 6)

Urine No.	Date	Total N	Urea N Gm.	NH_3N, Gm.	Cr_1N, Gm.	Cr_2N, Gm.	Total Purin N, Gm.	Formo. Titr. N, Gm.	Undet. N, Gm.	Urea N, Per Cent	NH_3N, Per Cent	Cr_1N, Per Cent	Cr_2N, Per Cent	Total Purin N, Per Cent	Formol Titr. N, Per Cent	Undet. N, Per Cent
1	Oct. 23-24	8.06	6.02	0.45	0.31	0.0	0.31	0.41	0.66	74.7	5.6	3.9	0.0	3.9	5.1	6.8
2	Oct. 26-27	11.09	8.37	0.62	0.43	0.0	0(?)	0.78	0.94	75.5	5.6	3.9	0.0	...	6.6	8.4
3	Oct. 27-28	7.90	6.31	0.46	0.31	0.0	0.28	0.40	0.14	79.8	5.2	3.9	0.0	3.5	5.0	2.6
4	Oct. 28 (labor)	0.45	0.34	0.03	....	....	....	....	....	75.6	7.5	...	...	...	...	...‡
5	Oct. 29 (14 hours after delivery)	0.41	0.30	0.03	....	....	....	....	....	73.2	7.0	...	...	...	...	...†
6	Oct. 29-30	4.87	3.61	0.11	0.25	0.0	....			74.1	2.3	5.2	...	...	...	...*
7	Oct. 31-Nov. 1	4.42	2.29	1.38	0.40	0.0	0.08	0.16	0.11	51.8	31.2	9.1	0.0	1.8	3.5	2.6
8	Nov. 2-3	15.11	9.80	3.20	0.51	0.12	0.03	0.37	1.08	64.8	21.2	3.4	0.8	2.0	2.4	5.4
9	Nov. 4-5	15.73	11.07	2.42	0.46	0.08	0.06	0.45	1.19	70.4	15.4	2.9	0.5	0.4	2.9	7.5
10	Nov. 5-6	12.41	9.02	2.03	0.36	0.06	0.06	0.31	1.60	72.7	16.4	2.9	0.5	0.5	2.5	4.5

* First twenty-four hours' urine after convulsions. † Urine fourteen hours after convulsions began. ‡ Urine just before convulsions.

This patient was pre-eclamptic and immediately following her delivery had convulsions. There was no change in the urea and ammonia fractions until 24 hours after the convulsions began.

TABLE IV

ECLAMPSIA

Case No.	Date	Amount Grams			Per Cent		Case No.		Amount Grams			Per Cent	
		Total N	NH_3N	NH_2N †	NH_3N	NH_2N			Total N	NH_3N	NH_2N *	NH_3N	NH_2N
7	Oct. 20-21, 1911	12.01	2.22	0.38	18.5	3.2	8	May 2-3, 1912	8.74	0.60	0.06	6.8	0.7
	Oct. 21-22, 1911	6.51	1.10	0.18	16.9	2.8		May 3-4, 1912	16.27	0.63	0.17	3.8	1.0
	Oct. 24-25, 1911	8.26	0.32	....	3.9	...		May 4-5, 1912	12.80	0.60	0.27	4.7	2.1
	Oct. 28-29, 1911	11.96	0.53	0.34	4.4	2.8		May 5-6, 1912	12.03	1.06	0.43	8.8	3.6
	Nov. 4-5, 1911	5.88	0.20	0.15	3.4	2.5		May 6-7, 1912	8.52	0.46	0.12	5.4	1.4

† Method of Henriques and Sörensen.

* By new method of Benedict and Murlin.

Case No. 7 had a marked increase in the ammonia excretion at the onset of the convulsions, while case No. 8 had normal ammonia and amino-acid throughout, although she had 50 convulsions.

per cent, mono-amino acid nitrogen of 4.1 per cent and undetermined nitrogen of 4.0 per cent. The purin nitrogen was 3.2 per cent. If these last fractions are added they will account for more than 11 per cent of the total nitrogen. After the administration of a cathartic to one of the normal pregnancy cases, the ammonia figure, while remaining the same in absolute amount, was raised to 17 per cent, owing to the reduction in the total nitrogen excreted.

In studying case No. 6, Table III, who was preëclamptic, the urine was obtained for three days and then as labor occurred true eclampsia with convulsions developed. Specimens were obtained just before the spasms, during the attack and for the entire 24 hour period. There was no deviation from the normal in any of the nitrogen fractions until the second 24 hour period, when the ammonia became high in both absolute and relative amounts and remained so. It was noted, however, that there was an absence of acetone and diacetic acid. Case No. 7, Table IV, had a total of seven convulsions and the ammonia was high for the first 48 hours but the amino-acids were normal. Case No. 8 had between 40 and 50 convulsions but the ammonia and amino-acids were not increased.

These authors, having been impressed by the high ammonia figures in a fatal case of pernicious vomiting, who had apparently in the latter part of an illness lasting a month, developed a terminal infection of the kidneys, arrived at the conclusion that some of the high figures for this fraction were caused by a foul bladder. As Folin remarked in another connection, the formation of ammonia in the large intestine; "Nothing is more simple than the growth of Bacillus coli communis in an albuminous media in the absence of carbohydrates." These conditions may be present in the bladder and lead thus to the breaking-up of protein. In two cases of normal pregnancy with infected bladders and high ammonia fractions, a decided reduction in the ammonia followed the washing of the bladder with boric acid, the diet and the total nitrogen in the urine remaining the same. The reduction in one instance was from 2.27 gms. with the total nitrogen of 14.71 gms. to 1.33 gms. with the total of 14.08 gms.

Losee and Van Slyke present the most interesting figures in cases of pernicious vomiting. There is a very low urea and high ammonia and undetermined nitrogen fraction and so far the results are quite in accord with Ewing's and Williams' figures. The authors mention that these amounts suggest those obtained by Nencki and Pawlow in a dog whose liver had been removed. However, the amino-acid nitrogen is normal and the carbon dioxid combining power of the blood plasma in two instances is 62 and 52, showing no acidosis, and 41 in the last case, representing a slight acidosis.

For comparison with these figures there is the recent report of Stadie and Van Slyke of the urine and blood findings of a woman who was not

TABLE V

PLASMA BICARBONATE AND NITROGEN DISTRIBUTION OF URINE IN PERNICIOUS VOMITING. (Losee & Van Slyke)

HISTORY	URINE						C.C. OF CO_2 BOUND BY 100 C.C. OF PLASMA
		PER CENT OF TOTAL N AS:					
Para, Months Pregnant, etc.	Total N. gm. per 100 c.c.	Alb.	Urea	Ammonia	Urea Total Amino-acids	Undetermined	Mother's Blood
P. I, 3 mos. 140 b.p. vomiting 2 weeks; much emaciated	0.782	1.5	54.8	24.9	2.4	16.4	
P. II, 3 mos. Vomiting 1 week	1.020	.....	46.3	31.2	2.3	.....	62.
3 mos.	0.602	.....	55.4	27.4	2.3	14.9	
2½ mos.	1.645	.....	67.4	17.5	2.2	12.9	52.
3 mos.	1.791	.....	64.1	16.9			
P. II, 2½ mos. vomiting 4 weeks; condition bad	0.928	trace	51.1	29.0	2.9	17.0	41.

pregnant but who had an almost complete destruction of the liver from acute atrophy. There was a reduction in the urea of the urine to about 50 per cent of the total nitrogen and an increase of the ammonia to 16, 17 and 11 per cent for the fifth, fourth and third days preceding death. There was also a high amino-acid excretion, 4, 16 and 13 per cent, and an increase of the undetermined nitrogen to 32, 8, and 23 per cent for this same period. On these days there was no fall of the plasma bicarbonate and the urea of the blood was normal but the amino-acids were doubled in amount. On the day before death no urine was obtained because of the condition of the patient but the blood urea was 15.9 mg. and the amino-acids were 26.3 mg. per 100 c.c. The plasma bicarbonate was reduced to 49 c.c. showing only a slight acidosis. They believe that there was an increase of the amino-acids by autolysis in the atrophying liver and a failure to deaminate them at even an ordinary rate and that the figures support the view that the liver bears a part in the deamination of amino-acids and the synthesis of urea, which cannot be entirely assumed by the rest of the body. They indicate that they accept the theory that there is a "factor of safety" as regards function in liver degeneration and that amino-acids are increased in the blood and urine only when the destruction of the liver cells is almost complete.

Examination of the Blood by Modern Methods

In 1912 Folin and his coworkers developed microchemical tests which require only small amounts of blood for a complete study. The new work of Folin and Denis(*a*) and of Van Slyke and Meyer(*a*) show that neither the intestine nor the liver has more to do with the deamination of absorbed protein than have other tissues. If these demonstrations are not controverted, then high amino-acid nitrogen cannot be charged entirely to defective functioning of the liver. It might be well to mention that as there is a deamidase in the placenta capable of splitting placental protein, it is possible that this source is the origin of the excretion of amino bodies in the maternal urine.

Farr and Williams examined the nitrogen in the blood of 12 normal cases of pregnancy and found the non-protein nitrogen to average from 20 to 30 mg. per 100 c.c. and the urea to vary from 6 to 10 mg. In 11 cases representing the kidney of pregnancy and preëclampsia or, in other words, with renal symptoms of a mild nature, the non-protein nitrogen varied from 29 to 52 mg. and the urea from 7 to 30 mg. In 13 eclamptics the non-protein nitrogen ran from 25 to 72 mg. and the urea from 11 to 50 mg. They conclude that the degree of retention in women with renal changes corresponds to that seen in chronic parenchymatous nephritis.

Bock, and Cullen, Ellis and Van Slyke determined that the normal, amino-acid content of the blood was from 4 to 8 mg. per 100 c.c. Losee and Van Slyke in examining 11 cases of eclampsia found a normal amino-acid amount, the figures varying from 4.4 to 7.9 mg. Their figures for the non-protein nitrogen and the urea nitrogen fell within those noted by Farr and Williams. Slemons agrees with Losee and Van Slyke that in eclampsia and nephritic toxemia the amino-acid values are generally normal. He noted in three cases of obscure toxemia without albuminuria an increase amounting to from 15 to 21 mg. and thought that possibly these toxic cases were related to acute yellow atrophy.

In the collected figures of some 30 cases of eclampsia of the last three observers there are none with an abnormal amino-acid content in the blood and it would appear that the theory of defective deamination does not apply in this disease. However, there are evidences in the accumulation of other substances that the liver does not function normally in this condition.

In the metabolism of creatinin, one of the striking features is that it is remarkably constant for any one individual and quite independent of the ordinary protein metabolism. The same may be said of the catabolism of the nucleic acid to form uric acid. The kidney has a limited power of excretion for both creatinin and uric acid and any increase above this leads to a retention and accumulation in the blood. As regards the uric acid, this retention is easy to demonstrate by feeding such a substance as

sweetbreads, whereupon there is an immediate accumulation of uric acid in the blood.

An analysis by Gettler of the blood of several eclamptics on the Bellevue service showed a definite increase in the uric acid content with a slight increase in the urea and non-protein nitrogen.

A most extensive study of this subject has been made by W. E. Caldwell and W. G. Lyle. Working with material from Bellevue and the Nursery and Childs Hospitals they examined the blood in 150 cases of normal pregnancy and of a number of nephritic toxemias and eclamptics. This work is now in preparation for publication and through courtesy they have permitted me to review their findings and to present the tables that follow.*

These 150 cases of normal pregnancy not only form the foundation for comparison but they are of particular interest because they show very low urea fractions. The average for the entire series shows a non-protein nitrogen of 29.6 mg., urea of 11.5 mg., creatinin of 1.0 mg. and uric acid of 1.7 mg. per 100 c.c. The urea nitrogen ratio to non-protein nitrogen is 39 per cent. The comparison for the different months of pregnancy would indicate that there is a slight increase in all the fractions in the ninth month, the non-protein nitrogen for 12 cases rising to 33 mg. and the urea to 12.6 mg. This occurs at a time when the fetus is growing rapidly and the increase of the total nitrogen may represent the provision of a floating reserve.

If the results of those cases that had a toxemia of the nephritic type and without convulsions are studied, gradual deviation from the normal may be noted and quite in accordance with the clinical symptoms. There were two cases (Nos. 1 and 2, Table VI) that had a trace of albumin in their urine but with no other symptoms and represent the "kidney of pregnancy." The creatinin and uric acid components were slightly above normal.

There is nothing distinctive about the figures of Case 3, Table VI, but the urea is somewhat high. The same may be said of Case 4, in the findings 22 days before delivery, but in addition there was a marked increase of the uric acid. A second specimen showing further increase in the urea and the blood picture fitting the clinical symptoms, led to the induction of labor which resulted in a stillbirth. In the blood taken five days after delivery there is a marked decrease in the urea content. Case 5 is definitely abnormal and the specimen taken 14 days after delivery places it in the class of chronic parenchymatous nephritis. Cases 6 and 7 were both received at the hospital in a comatose condition and without history of having had convulsions. They died without regaining consciousness and appeared to be typical cases of uremia. The blood picture of Case 6

* Since the writing of this article Caldwell and Lyle have published their work. See Bibliography.

TABLE VI

TOXEMIA, NEPHRITIC TYPE. (NO CONVULSIONS.) (Caldwell and Lyle)

No.	Week of Gestation	Name	Date, 1918	N. P. N.	Urea	Creatinin	Uric Acid	Delivered	Note
1.	38th	R. E.	6/12	27.3	9.4	2.1	3.2	6/12	Trace alb.
2.	38th	S. H.	8/2	26.7	8.7	1.2	2.8	8/17	Trace alb.
3.	38th	J. D.	2/15	30.2	14.4	1.9	1.3	2/28	Heavy alb. casts, blood pressure 142
4.	28th	K. G.	4/3	39.6	15.5	1.0	8.0	4/25	Heavy alb.
			4/23	39.7	17.3	0.9	3.9		stillbirth, casts,
			4/30	*39.6*	*7.2*	*1.0*	*2.1*		blood pressure 200
5.	28th	M. G.	5/31	53.3	31.7	3.1	4.7	6/2	Heavy alb.
			6/3	36.7	19.5	1.6	4.3		casts, blood
			6/16	*44.0*	*21.6*	*1.7*	*8.9*		pressure 180
6.	32nd	M. C.	6/9	106.0	80.0	6.5	8.7	6/10	Heavy alb.
			6/11	116.0	86.0	6.6	9.1		stillbirth, casts, blood pressure 120, coma, died
7.	36th	L. C.	6/1	63.0	34.6	4.8	8.0		In coma, died undelivered

(NOTE.—Figures in italics represent the control test 4 days or more post partum.)

is typical of chronic nephritis but the figures of Case 7 show less retention than is usually found in uremia and are similar to those of convulsive eclampsia.

This table offers direct evidence of the value of blood determinations for diagnosis and also for prognosis. The trend of the figures is in relation to the severity of the clinical symptoms.

In 12 typical eclamptic cases, it was found that they all had albumin and casts in the urine and a high systolic blood pressure. Eight of the cases recovered and therefore the observer was able to procure more than one blood specimen in most instances. The first three cases show very slight changes in the partitions. Case No. 1, Table VII is quite normal except for the rise in the uric acid. The next two cases have, in addition to the increase in the creatinin and uric acid, a slight rise in the urea. All the others have an increase in the figures, but not as marked as is usual in chronic nephritis, except Case No. 9 which has a retention of the urea. The urea figures in Caldwell and Lyle's cases are somewhat higher than those presented by Slemons and by Losee and Van Slyke and are more in accord with those of Farr and Williams. As many cases on recovery show higher figures than others do at the time of their convulsions; and as many chronic nephritic cases show higher figures without any increase in their clinical symptoms, it becomes evident that these changes are the result rather than the cause of the toxemia leading to eclampsia. Of seven of the eclamptic cases that recovered a follow-up examination after two years shows that Cases 3 and 6 are normal from a clinical stand-

point and a blood analysis of Case 6 shows no evidence of nitrogen retention. Cases 4, 5, and 7 have again passed through a pregnancy and puerperium with no albumin in the urine and with no abnormal signs.

Nitrogen of the Blood

TABLE VII

TYPICAL ANTEPARTUM AND POSTPARTUM ECLAMPSIA. (Caldwell and Lyle)

No.	Period	Name	Date	N. P. N.	Urea	Creatinin	Uric Acid	Delivered	Result	
									Mater.	Inf.
1.	9 mos.	E. S.	1/4 1/5	31.0 31.6	10.8 10.9	1.3 1.2	4.8 4.8	1/5	Recov.	S. B.
2.	9 mos.	S. L.	9/4	34.6	13.6	2.4	5.0	9/3	Recov.	L. B.
3.	7 mos.	H. H.	8/3 8/5 *9/15*	35.3 35.0 *45.5*	15.7 14.4	3.1 3.1 *0.9*	5.1 5.0	8/2	Recov.	S. B.
4.	8 mos.	L. F.	3/19 *3/25*	52.1 *39.0*	25.5 *15.1*	1.2 *0.9*	6.1 *2.8*	3/19	Recov.	S. B.
5.	9 mos.	R. F.	7/8 7/9 *7/12*	44.0 50.3 *21.0*	17.3 23.1 *11.5*	.... 5.4 *3.8*	5.0 7.2 *6.6*	7/8	Recov.	L. B.
6.	7 mos.	H.	6/10 7/1 7/8	50.5 60.0 *34.6*	32.4 40.4 *16.6*	1.3 2.0 *1.4*	10.0 11.0 *7.2*	7/1	Recov.	L. B.
7.	8 mos.	E. B.	5/30 *6/7*	51.2 *41.1*	25.2 *21.4*	2.8 *1.7*	6.7 *2.5*	5/29	Recov.	L. B.
8.	7 mos.	R. C.	3/11	58.5	34.5	1.0	5.8	3/11	Insane	L. B.
9.	6 mos.	E. B.	2/18	83.6	63.8	4.0	7.6	2/17	Died	S. B.
10.	6 mos.	J. N.	2/18	51.7	25.2	1.1	4.0	2/20	Died	S. B.
11.	.....	L. M.	12/2	57.0	32.4	1.8	3.5	....	Died	
POSTPARTUM ECLAMPSIA										
12.	Form F.	....	7/5	42.5	18.7	4.2	11.3	7/2	Convulsions 3 days post partum Died	L. B.

(NOTE.—Figures in italics represent the control test 4 days or more post partum.)

Quite in contrast to Caldwell and Lyle's results are those of J. A. Killian.* Working in Myer's laboratory, he analyzed the blood of a

* Paper read at the New York Pathological Society, February 9, 1921. The author has very kindly permitted me to use his tables. Since the writing of this chapter, the work has been published by Killian and Sherwin.

number of eclamptics and besides ascertaining the nitrogenous constituents he found also the percentage of sugar, chlorid concentration and the carbon dioxid combining power. He separates the cases into two groups, the Hepatic and the Nephritic Toxemias. In the former there is little evidence of nitrogen retention and the urea fraction is low so that compared with the non-protein nitrogen the coefficient is from 0.15 to 0.38. In the latter just the reverse is true and the coefficient is 0.50 or above.

In the table entitled Hepatic Toxemia the first two blood examinations were from typical cases of pernicious vomiting. The results are interesting for they furnish absolutely new evidence concerning this disease and support the deamination theory. With a normal or slightly lowered urea there is an increase in the non-protein nitrogen producing a very low ratio—0.33 in the first case and 0.15 in the second. In the former there is a marked acidosis represented by 28 c.c. carbon dioxid combining power and in the latter by 42 c.c. In the absence of amino-acid determinations one may only conclude that there is either a failure of deamination of amino bodies or failure of oxidation of more complex portions of the protein molecule. Withdrawal of ammonia for combination with these amino bodies would lead to a reduction of the blood acidity. A sort of "spurious acidosis" as Ewing terms it. These figures support the urinary findings in Ewing and Wolf's, and Losee and Van Slyke's vomiting cases, especially as regards the high ammonia and the high undetermined nitrogen.

Of the 17 eclamptic cases three died (Cases 4, 7, and 12, Table VIII) and in these three cases there was only a slight rise in the non-protein nitrogen with a low urea so that the coefficients were 0.32, 0.36, and 0.29 respectively. There was marked acidosis in most of the cases and in Case 12 there was a carbon dioxid combining power of only 12 c.c.

Of the other 14 eclamptic cases there were 12 that had a non-protein nitrogen figure below 50 mg. and the ratio with the urea of 0.35 or under, although in three cases the ratio was as low as 0.16. The uric acid was increased and in a few instances so was the creatinin. In all the cases there was a slight increase of the blood sugar but this was also noticed in normal pregnancy. Those cases that showed considerable edema were found to have an increased concentration of the chlorids of the whole blood and in all cases where the chlorids were above 0.50 per cent the urine was very heavy in albumin.

A study of these results leads to the conclusion that there was failure of the liver to respond with increased urea formation and the relationship of the known fractions together with the results of other analyses would indicate that undetermined nitrogen of the blood is not amino-acid but some as yet unknown metabolite of the nature of a higher protein. In these eclamptic cases there is but slight evidence of insufficiency of the kidneys as regards the nitrogen excretion. In Cases 18 and

TABLE VIII

HEPATIC TOXEMIA. (Killian and Sherwin)

Case	Age	Para	Mos. of Gest.	Blood Analyses								Urine		Blood Pressure		Remarks
				N. P. N.	Urea N	Urea N / N. P. N.	Uric Acid	Creatinin	Chlorids	Sugar	CO_2 C. P.	Protein	Casts	Systolic	Diastolic	
1. C. B...	22	I	3	34	12	0.33	3.0	1.9	0.47	0.12	28	+	—	130	90	Pernicious vomiting. No convulsions.
2. N. O...	27	II	3	56	8	0.15	.....	1.6	0.41	0.14	42	+	—	110	70	Pernicious vomiting. No convulsions.
3. B. W...	25	I	9	30	5	0.16	8.5	.....	0.63	0.10	16	+++	—	165	100	Postpartum eclampsia. Convulsions began three hours after parturition.
4. M. B...	21	I	9	36	11	0.32	4.8	1.9	.....	0.15	.....	.....	.....	195	105	Postpartum eclampsia. Convulsions began one hour after parturition. Died.
5. J. H...	29	II	7	37	10	0.27	3.8	.....	0.59	0.09	42	+++	—	185	110	Postpartum eclampsia. Convulsions began two days after parturition.
6. H. S...	22	I	9	48 26	15 13	0.32 0.50	7.3 3.5	1.8 2.1	0.46 0.50	0.13 0.12	28 40	++++ +	— +	190 100	100 65	Postpartum eclampsia. Convulsions began two hours after parturition. 14 days later. Control specimen.
7. M. E...	27	I	7	34	13	0.36	11.0	2.5	.....	0.13	38	+++	—	210	140	Severe convulsions for twelve hours previous. Cesarean. Died 24 hours later. Stillbirth.
8. Y. H...	28	I	7½	35 23	9 12	0.27 0.51	6.8 2.5	....	....	0.12 0.09	38 53	++ —	— —	190 —	130 —	Severe convulsions for four hours. Cesarean, Stillbirth. 5 days later. Control specimen.
9. M. B...	29	III	7½	36	9	0.22	4.5	1.9	0.52	0.12	26	+++	—	175	105	Convulsions for four hours. Slight edema.
10. B. R...	33	I	9	36	12	0.34	3.6	1.7	0.47	0.16	34	++	—	140	84	Two convulsions. Mild case.
11. H. B...	32	III	7	37	14	0.34	6.5	.....	0.58	0.10	40	++++	++	.....	.....	Convulsions four hours. Marked edema. Stillbirth.
12. F. H...	27	I	7	38	10	0.29	3.4	1.9	0.61	0.10	12	++	+	.....	.....	Convulsions for two hours. Died. Marked edema. Stillbirth.
13. E. R...	19	I	7½	39	12	0.30	7.5	2.3	0.47	0.13	40	++	—	150	115	Severe convulsions. Fetus; died.
14. R. W..	24	II	8	40	6	0.16	6.8	2.5	0.55	0.13	36	++++	+++	164	100	Severe convulsions for 4 hrs. Moderate edema. Stillbirth.
15. E. P...	20	I	7½	40	6	0.16	6.8	2.2	0.52	0.12	30	++	—	185	100	Very severe convulsions. Fetus macerated. Slight edema.
16. N. L...	24	II	7	47	14	0.29	5.4	.....	0.63	0.12	.....	++++	++	220	118	Severe convulsions twelve hours. Stillbirth. Marked edema.
17. A. B...	21	I	9	50	9	0.18	5.6	2.2	0.52	0.18	21	+++	++	160	85	Severe convulsions. Slight edema.
18. M. R...	21	I	7	56	22	0.38	6.8	2.7	0.52	0.11	20	++++	—	195	110	Convulsions for twelve hours. Stillbirth.
19. B. S...	26	I	6½	64	22	0.32	8.6	2.5	0.42	0.10	.....	++	—	210	110	Very severe convulsions for twelve hours.

19 the increase in the urea to 22 mg. together with the high uric acid would indicate that there is a secondary functional renal disturbance.

Changes of the Urea Nitrogen in the Blood

In studying the urea variations it is well to remember that in eclampsia it represents to a large extent the endogenous metabolism, for at the time that the bloods were collected little or no food was taken and in all the toxemic cases protein was eliminated from the diet. While urea is a very diffusable substance, passing rapidly through such an organ as the placenta, it is probable that there is a limitation on the part of the kidneys as to the amount that can be excreted. The substance itself, however, is a diuretic and has even been used as such by Pinard. It is easily proven that it does not produce convulsions, at least in any ordinary amount. Hewlett and Wickett have recently found that when 100 to 125 mg. of urea is given to normal men they develop symptoms similar to asthenic uremia, which appear only when the urea retention reaches 160 to 245 mg. per 100 c.c.

In the non-pregnant renal efficiency is evidenced by a $\frac{\text{urea}}{\text{N.P.N.}}$ of 0.50. Mosenthal and Hiller have shown that any functional disturbance leads to an increase of the urea and consequently to a rise in the coefficient.

Lyle's figures for the urea nitrogen in the blood in 5,000 women show 18 mg. or less but in the pregnant state it averages, in his cases, 11.5 mg. Folin found that it ran as low as 5 to 9 mg. In the non-pregnant, Folin and Denis placed the normal from 12 to 17 mg. and Gettler and Baker in a series of 30 cases found 15 to 25 mg. per 100 c.c.

In the 8 cases of eclampsia that recovered in Caldwell and Lyle's chart, there are only 2 cases that surpass these normal figures of the non-pregnant and of the 4 fatal cases (9, 10, 11 and 12 of Table VII) there were 2 that were higher.

When we come to compare Caldwell and Lyle's eclamptic cases with those of Killian from the standpoint of urea-non-protein nitrogen coefficient, their cases (Nos. 1, 3, and possibly 12) would fall into the class called hepatic toxemias by Killian and the remainder under the caption of hepatic toxemias accompanied by renal insufficiency. In hepatic toxemias the urea is not only low and considerably lower than in the normal individual but in a few instances it is lower than the average in pregnancy. The explanation for this low figure, taking into consideration the increased non-protein nitrogen must be that there is a failure on the part of the liver to respond to a flux of nitrogenous bodies with an increased urea synthesis. It is unfortunate that these more recent observ-

ers have not included the amino-acids in their analyses. Losee and Van Slyke have given the amino-acid figures as 4.4 mg. to 7.9 mg. for this disease. If this figure or a figure somewhat higher, as 10 mg., is taken as a fair average it will be seen that there is a rest or undetermined nitrogen in the blood which, if it is justifiable to rule out the amino-acids on the strength of these other analyses, must be a metabolite of the form of oxyproteic acid or more complex form of protein. It would seem reasonable to suppose that in this disease with the chief and most constant pathological lesion occurring in the liver that there is a failure on the part of this organ to break up these metabolites to simpler forms. The withdrawal of the ammonia to neutralize these substances leads to a low carbon dioxid combining power of the blood or to a condition of acidosis which in many respects is quite different from the acidosis present in such conditions as diabetes or starvation.

There are three possible explanations for the rise of the urea.

1. It represents the inability of the kidney to excrete urea even at a normal rate and shows a functional disturbance of this organ.

2. Amino-acids or other proteolytic products formerly passing through the placenta for the use of the fetus are refused or cease to pass through that organ and therefore remain in the maternal organism and are deaminized to urea.

3. Catabolic products from autolysis of degenerated cell areas in the liver, kidneys and placenta or from syncytial cell infarcts occurring in the convulsive period are converted to urea.

Increase in the Creatinin Nitrogen in the Blood

Creatin and creatinin metabolism are independent of the exogenous protein metabolism when flesh is excluded from the diet. Creatin is related to the mass of muscular tissue and exists in the muscle plasma. It is changed by anhydration to creatinin and this occurs either in the muscle or in the liver, the latter organ being usually credited with this function. Ordinary muscular work does not influence the excretion of the creatinin, but excessive muscular action in inanition or rapidly wasting disease increases both the creatin and creatinin output.

Creatin appears in the urine of the latter part of pregnancy and creatinin exists in increased amounts. The increase of the creatin was explained by Von Hoogenhuyze and Ten Doeschate as an evidence of hepatic insufficiency, but as Murlin(*b*) states this would call for a decrease in the creatinin excreted. As there is an intimate relationship between the carbohydrate and creatin metabolism, the latter author adopts a similar explanation to that suggested by Mendel and Rose for the presence of creatin in the urine of growing children. An actual deficiency in carbo-

hydrate in the maternal circulation because of the rapid diffusion of dextrose through the placenta leads, indirectly, to an increased elimination of the creatin. If we reëxamine the charts of Ewing's pernicious vomiting cases, where the supposition is reasonable that a liver degeneration existed, we will find that there is no increase in the actual amount of creatinin in the urine. The same statement does not hold for the excretion of creatin in the experimentally produced degeneration in the dog to which hydrazin was administered by Underhill and Kleiner. Here, while the creatinin excretion was variable, there was a relatively large output of creatin. In the delayed chloroform poisoning in dogs, Howland and Richards found that the creatin was increased in both dogs that were severely poisoned but not in the control animal.

Wolf and Osterberg in their experimental degeneration of the liver in dogs by means of phlorizin found a marked increase in the creatin output and suggested that it might be due to the increased formation of creatin or to the inhibition of the processes whereby creatin is converted into urea. It was formerly held that creatin and uric acid were converted to urea in an unknown but definite proportion of their entire amount.

Ten of the total of 19 cases of eclampsia in Caldwell and Lyle's list show an increase to 2 mg. in the creatinin content of the blood. Of itself this fact might be considered of only moderate importance for so little is known of the metabolism of creatin and creatinin. It demands attention for in conjunction there is marked retention in the uric acid, representing nuclear metabolism, and the kidneys are also eliminating considerable amounts of these substances.

Attention should be given to the ability of the kidney to excrete creatinin. Orlovius found that the excretion in normal pregnancy averaged for 11 cases 1.23 gm. and that the kidney function could be estimated by the time limits necessary for the elimination of stated amounts of creatinin, administered by intramuscular injection. Normal kidneys eliminate 1.5 gm. in 12 hours and degeneration of the kidneys leads to a slow excretion lasting over 24 hours. In the non-pregnant the elimination is from 0.7 to 1.1 gm. per kilogram of body weight.

In chronic nephritis there is an increase in the creatinin fraction in the blood and it would appear that it is the last of the metabolites to be retained by the kidneys. In nephritis, however, there is a lessened output in the urine.

To summarize the theories accounting for the increase of creatin and creatinin in the urine and the increase of creatinin in the blood, they are as follows:

1. Retention from inability of a damaged kidney to excrete creatinin.
2. A supply of creatin from the fetus which is synthesized.

3. Increase of creatin by the rapid degeneration of muscle tissue, owing to the inanition and also to the convulsions.

4. Decrease in the amount of circulating carbohydrate from defective glycogenic function, or from the withdrawal of dextrose for the needs of the fetus, leads to a rise in the creatin production which is in turn converted to creatinin.

Increase in the Uric Acid Nitrogen in the Blood

Uric acid represents the results of purin metabolism and is derived from the breaking down of nuclear material. When meat is excluded and no purin bodies are ingested, the endogenous uric acid metabolism represents the product of the synthesis of the nitrogen of the broken down cell. Like creatin, it is a special metabolism not directly related to the metabolism of the proteins.

As most observers agree that uric acd is one of the first nitrogenous substances to be retained in the blood in degeneration of the kidney and as there seems to be a definite limitation as to the amount that can be excreted at any one time, it is possible the increase in this substance only represents a functional disturbance on the part of the kidney. In eclampsia, however, there may be an increase of nucleic acid derived from autolysis of the degenerated cell nuclei in the liver and kidney.

There is a large amount of uric acid in the tissues of the fetus that is rapidly excreted following birth and it is possible that some of this substance passes through the placenta to the mother. Slemons and Bogart found an increase of the blood uric acid at the end of labor.

It has been known from studies of gout that the threshold is raised by an increased content in the blood. In the various types of nephritis there is a lessened uric acid excretion in the urine with a consequent increase in the blood.

In Caldwell and Lyle's eclamptic cases the uric acid content ranged from 3 to 11 mg. per 100 c.c. of blood but the average was 6 to 7 mg. In Killian's cases, also, the figures varied from 3 to 11 mg. and the average was 6 mg.

Other Evidences of Disturbed Metabolism

Blood and urine examinations offer evidences of disturbed metabolism other than those referable to the nitrogen. Glycosuria has been noted in pregnancy by a number of observers. Geelmuyden(*a*) states that it occurs in 10 to 12 per cent of all pregnancies. An alimentary glycosuria can readily be produced in the pregnant by administering 100 gm. of glucose.

Following this test Reichenstein found sugar in the urine of 37.5 per cent of the cases and his results have been thoroughly verified by others. Widen in an examination of the blood in eight cases of eclampsia found the hyperglycemia to be variable and its absence denoted a serious prognosis. He stated that the sugar content was also increased in pernicious vomiting. Morriss found values of 0.098 to 0.116 per cent for normal pregnancy and no increase in the sugar in pre-eclampsia. In 5 eclamptics the figures were 0.097 per cent, 0.128 per cent, 0.136 per cent, 0.151 per cent and 0.256 per cent. The blood specimens were all obtained directly after a convulsion. Killian found a moderate hyperglycemia in all of his eclamptic cases.

These figures are in contrast to those obtained in uremia and chronic nephritis, which are invariably higher and this fact may be made use of in differentiating between the two diseases.

Falco experimenting with pregnant rabbits and guinea pigs found histological evidence in the islands of Langerhans of pancreatic insufficiency. He suggested that the placenta takes some part in the carbohydrate metabolism.

Increase in the cholesterol content of the blood in normal pregnancy and a considerable increase in eclampsia have been noted by Autenreith and Funk, Slemons, and Pisani and Savare. It has long been known that there is an increase in the cholesterol of the pregnant and its deposition in the liver has been accepted as an explanation of the frequency of gallstones in women. It has been suggested that the cholesterol determinations may prove of value in separating the eclamptic from the nephritic toxemias.

J. C. Litzenberg in a study of 271 cases of pregnancy found urobilinogen or urobilin in the urine in 25 per cent and points out, that in the absence of blood destruction it indicates an insufficiency of the liver.

Summary

Experimental studies in animals whose livers were removed or sidetracked by means of the Eck fistula showed high ammonia in the urine when protein was fed to them. Animals with liver degeneration following the administration of various toxic substances showed little or no increase in the ammonia in the urine; and it has been suggested that under such conditions there is a safety mechanism operable, whereby the undamaged cells take on an increase in activity.

Pernicious vomiting and acute yellow atrophy cases markedly resemble, as regards the nitrogen excretion in the urine, the animals in the experimental studies. There are instances in which the changes are so slight as to suggest that the liver degeneration was not extensive. In other cases

there have been found marked changes in the urea and ammonia excretion. Recent blood determinations of the carbon dioxid uniting power, representing the degree of acidity, would indicate that even in the presence of the high ammonia in the urine, there is no lessening of the alkali reserve. The amino-acid of the urine may be normal in amount in the presence of this high ammonia output. These conflicting results leave no explanation for the rise in ammonia unless it occurs in the bladder from bacterial action.

However, there are on record two cases of pernicious vomiting in which the blood chemistry and carbon dioxid combining power have been obtained and both show a low urea coefficient with marked acidosis. The undetermined nitrogen constituent is left unexplained but there is indication that it consists of amino bodies. The remarkable similarity of the blood picture of pernicious vomiting and eclampsia adds confirmation to the theory of the single identity of these diseases. Further blood determinations especially of the amino-bodies are needed.

Stadie and Van Slyke's case of acute yellow atrophy in a non-pregnant woman would indicate that autolysis of this organ in vivo throws into the circulation an amount of amino-acids that cannot be taken care of by the tissues and hence deficient deamination becomes a fact and there results an increase of these bodies in the blood and urine.

In eclampsia the amino-acids of the blood and urine are not increased. There are changes in the non-protein nitrogen, the urea, the creatinin and uric acid fractions in the blood that point to an insufficiency of the liver and in many cases to a secondary functional disturbance of the kidneys as well. That liver degeneration may account for these changes, independently of lowered kidney function, is indicated in eclampsia by changes in the glycogenic, bile and lipoid functions of this organ.

Blood chemistry is of value in separating the chronic nephritic toxemias from the true eclampsias and in either condition may present evidence of disturbed metabolism that would indicate the necessity of emptying the uterus. The time of operative procedure must be made dependent upon the degree of acidosis as represented by the carbon dioxid combining power of the blood.

Diabetes Insipidus . . . . . *John R. Williams*

Historical—Prevalence—Etiology—Syphilis—Pregnancy—Symptoms and Signs—Pathological Anatomy—Prognosis—Diagnosis—Differential Diagnosis—Treatment.

Diabetes Insipidus

JOHN R. WILLIAMS

ROCHESTER

In the light of modern investigation, diabetes insipidus must be looked upon as a symptom complex or syndrome caused by some irritation or injury to certain areas of the brain as a result of which there is excited in the patient an excessive secretion of urine of low specific gravity and a profound degree of thirst. Numerous other symptoms and signs more or less inconstant are associated with the syndrome as weakness, slow pulse, low blood pressure, dry skin with absence of perspiration, regressive changes in sexual characteristics, and visual disturbances.

Clinicians have heretofore classified diabetes insipidus cases into two groups: the idiopathic group in which there are placed cases of unknown origin thought by some workers to be due to a disturbance in kidney function; and the symptomatic group which includes all cases associated with brain injury, whether due to trauma, infection, tumor or disturbed function. With our present understanding of the phenomena, it would seem as though this classification should now be abandoned.

Historical

A number of complete historical accounts of diabetes insipidus have appeared recently in the literature. Among the most interesting of these reviews is that of Fitz(*d*), to whose writings the author is indebted for many references. Thomas Willis (1621-1675), one of the great pioneers of the seventeenth century whose studies in brain anatomy are still remembered, was a keen clinical observer. He saw cases of diabetes which impressed him as being unusual and noted that the urine of these was quite different from that of true diabetes in that it lacked the characteristic sweet taste. He suggested this as a basis of differentiation.

About one hundred years later, Simmons in 1792 described two cases which are quoted at length in Fitz's article. These are the first to be published in English. The next reference to the disease was made by Johann Peter Frank (1745–1821) who in 1794 defined the malady as

"a long continued abnormally increased secretion of non-saccharine urine which is not caused by a diseased condition of the kidneys."

In the succeeding years, while occasional mention is made in the literature of the subject, no important contribution appeared until Claude Bernard(*b*)(1813-1878) published his studies on brain physiology. He demonstrated that by puncture of the floor of the fourth ventricle, a polyuria could be produced and he believed that he had discovered a center for diabetes insipidus. Later observations showed that polyuria may result from other lesions of the nervous system.

Many workers inspired by the studies of Bernard attacked the problem of determining the relation to normal physiological processes of various brain areas in and contiguous to the third and fourth ventricles. It was shown by Magnus and Schäfer in 1902 that extracts of the hypophysis when injected into an animal caused an increased secretion of urine. In 1916 Schäfer and Herring demonstrated that the diuretic principle of the hypophysis was in the pars intermedia. Cushing(*a*) and his associates (1908–1912) worked extensively with the hypophysis and noted among others things that after certain manipulations of the structure a severe polyuria followed which was sometimes of several days' duration. They directed attention to the similarity between this condition and diabetes insipidus. It was Cushing's conclusion that the syndrome was due to hypofunctioning of the hypophysis.

Prevalence

Diabetes insipidus is a very uncommon disorder or is seldom observed. Fitz reports a rate of occurrence of fourteen cases per hundred thousand from a statistical examination of 533,977 hospital and out-patient admissions. The author, in a similar study which includes chiefly well known American hospitals, found that 197 cases were observed in 1,935,770 hospital admissions, a rate of 19.2 per one hundred thousand. These data are shown in Table No. 1, page 863.

In many of the large general hospitals and clinics of this country, no cases have been observed. It is possible that the syndrome has been overlooked in some instances; on the other hand, it is probable that in the absence of precise methods of study, the disorder where diagnosed is sometimes confused with other diseases characterized by polyuria. Dr. L. G. Rowntree of the Mayo Clinic, Rochester, Minnesota, states that of a total of 257,000 admissions to the Mayo Clinic, 35 cases were indexed as diabetes insipidus. After a careful study of the data, eleven cases were discarded as being not true examples of the syndrome. Other well known clinicians, including George Dock and Joseph L. Miller, have expressed doubt as to the validity of the diagnosis in many cases and

TABLE NO. 1

Institution	Total Hospital Cases	No. Cases Diabetes Insipidus
Massachusetts General Hospital	206,171	28
Cook County Hospital, Chicago, Ill.	296,000	6
Barnes Hospital, St. Louis, Mo.	105,957	7
Mayo Clinic	257,500	24
Toronto General Hospital	80,000	5
Johns Hopkins Hospital	40,000	16
St. Lukes-Medical Dept., New York	3,917	4
University of Michigan Medical Dept.	6,686	2
Charity Hospital, New Orleans	196,467	9
Mercy Hospital, Pittsburgh	36,400	0
Mount Sinai, New York	28,523	4
Zurich Hospital	35,942	7
Charité, Berlin	113,600	55
Buffalo General	14,898	0
Los Angeles County Hospital	22,303	0
U. S. A. Base Hospital, Ft. Riley, Medical Service	60,000	3
New York Hospital	246,000	9
St. Francis Hospital, Pittsburgh	45,660	2
Harper Hospital, Detroit	3,860	4
University Hospital, San Francisco	108,188	3
Zion Hospital, San Francisco	7,898	4

as to whether the disorder should be considered a distinct disease entity. Since the condition is believed to be associated chiefly with brain lesions, one would expect to find it occurring frequently among the insane. This, however, does not appear to be the case. A survey of the records of the Kalamazoo State Hospital, Michigan, and a similar investigation of the records of the Rochester State Hospital, New York, reveal no authentic cases of diabetes insipidus.

Etiology

It has been noted by many workers that the syndrome occurs more commonly in the earlier periods of life than later. Of the 85 cases collected by Strauss, 9 were under five years of age, 12 were between five and ten years, and 36 cases were between ten and twenty-five years of age. Gerhardt(*a*) made a study of the cases in the literature in patients under ten years of age. Of these, 30 occurred before the age of five, and 30 between five and ten years. The condition has rarely been observed in infancy. Rachel reported 4 cases of the ages of four, five, ten and eleven months, said to have been afflicted with the syndrome. Several other doubtful or borderline cases in children have been reported.

Males are more commonly afflicted than females. This observation was first made by Stoermer in a series of 133 cases he had seen and from reports in the literature up to 1892. Moffet and Greenberger make the same statement with reference to children and report that of 36 cases

reviewed between the years 1888 and 1916, the proportion was 28 males to 8 females.

Earlier writers observed a familial tendency in the occurrence of diabetes insipidus which does not appear in recent literature. The most complete discussion of the subject from the standpoint of heredity is by Bulloch. He reviewed quite fully all the important cases which had been published up to 1909. A remarkable example of heredity was studied by Weil. He describes an individual born in 1772 who died in 1855 at the age of 83 years. His descendants were 5 children, 29 grandchildren, 66 great-grandchildren, 119 great-great-grandchildren, altogether 220 persons. Of these 220 individuals, 35 had diabetes insipidus: the founder of the family, 3 children, 7 grandchildren, 13 great-grandchildren and 11 great-great-grandchildren. There were besides, 16 doubtful cases, namely 9 grandchildren and 2 great-grandchildren who died young, and 5 great-great-grandchildren. The disease preponderated in the males but was transmitted by both sexes. One is impressed by the number of illegitimate children, 19 having been born out of wedlock. In addition there were 4 stillbirths and 2 idiots. In the absence of post mortem data, one can only speculate as to the probable disease which was transmitted and in this connection syphilis must be kept in mind, although Weil mentions only one of the total number as being thus infected.

Other studies are cited in Bulloch's article where in two or more generations of a family several cases of diabetes insipidus were said to have occurred. Ehrmann(*a*) describes an instance of the syndrome in a family of 5 children, 3 boys and 2 girls. The boys, aged respectively 8, 9, and 10 years, were all backward, one being an imbecile, whereas the girls were all bright.

There can be no doubt but that new growths of one kind or another involving the hypophysis or contiguous brain areas are responsible for many cases of diabetes insipidus. Frank(*c*) collected evidence on the etiologic relationship of tumor to the syndrome and cites five cases in which new growths involved the hypophysis or the infundibular region. As an illustration of metastases, Simmond's case occurred in a woman of 37 years, who a few months after operation for cancer of the breast developed an intense polyuria and thirst. At autopsy a small nodule was found involving the dorsum sella, the posterior lobe and the infundibulum. The pars intermedia and anterior lobes were apparently not involved. Barach states that cases have occurred after carcinomatous disease of the liver and suprarenals. In Finkelnberg's case at autopsy a cystic tumor was found at the bottom of the third ventricle between the chiasm and the hypophysis which was not enlarged. In Rosenhaupt's case, a sarcoma was found in the anterior lobe of the hypophysis and a similar growth in the thyroid. Newmark reports a case in a boy fourteen years of age who suffered for years with symptoms of diabetes insipidus. Two weeks

before death, a tumor was found occupying the region of the infundibulum extending forward through the lamina terminalis between the frontal lobes and backward into the third ventricle destroying the neurohypophysis and nearly all of the pars intermedia. Moffett and Greenberger report a case in a child of six years in which the X-ray examination revealed a shadow which was interpreted as a tumor involving the hypothalamus, but not disturbing the sella turcica. Cushing(*a*) described a case of a young man with a recurring lymphosarcoma of the neck and a metastatic growth in the thickened stalk of the pituitary. The patient had marked polyuria. He also reports another interesting case of a woman age forty years. The patient complained of blindness and headaches. A diagnosis of pituitary tumor and primary optic atrophy was made. There were symptoms of hypopituitarism. A sellar decompression operation was performed which provoked a severe postoperative diabetes insipidus which later moderated. The floor of the sella was thin and bulging. The hypophysis was found to be a dense mass containing a great increase of interstitial tissue. In view of the foregoing experiences, it is obvious that in the presence of the syndrome of diabetes insipidus, one should always bear in mind the possibility of a new growth in the region of the hypophysis, particularly if there be a preceding history of tumor and operation.

Severe injury to the head is undoubtedly the accountable factor in the production of the syndrome in some cases. The brain area about the hypophysis may be directly traumatized or pressure symptoms may result directly from the extravasation of blood into this region. As a rule, the symptoms of thirst and polyuria are very acute and severe, more so than when the causal agent is an infection or when the syndrome supervenes for unknown reasons. A case of Redslob's is cited by Frank in which a girl of fourteen years fell, striking her head on a stone floor and becoming unconscious. On recovery to consciousness she complained of defective vision and great thirst. After three months, examination of the eyes revealed bitemporal hemianopsia. The amount of urine voided daily was from 3,400 c.c. to 4,100 c.c. Later the polyuria improved but soon returned in increased amount. Frank reported a case of an obese male 39 years of age who entered the hospital because of epilepsy which came after an attempt at suicide. Several years before, the patient had fired two 7 mm. bullets into his right temple. The urine averaged six to seven liters daily. Sexual impotence and genital atrophy resulted, otherwise he was apparently physically sound. There were no eye symptoms. X-ray examination showed a bullet in the median line in the middle and posterior part of the sella turcica. This was encapsulated and acted as a permanent irritant to the pituitary body, producing a continuous diabetes insipidus and a certain degree of dystrophia adiposogenitalis.

The acute infectious diseases are occasionally responsible for a poly-

uria and polydipsia simulating diabetes insipidus. The nature of the process is not clearly understood, but it has been suggested (Moffett and Greenberger) that the hypophysis is affected directly by toxins of the infecting organisms. Tuberculosis, influenza, and syphilis are the most frequently mentioned infectious causative factors.

Syphilis.—Syphilis, particularly, has for years been associated with the syndrome. Fourier described it in 1871. Futcher called attention to the remarkable association of the two maladies in a report of nine cases of diabetes insipidus which he had observed, five of which were apparently due to a basilar syphilitic meningitis. Spanbock and Steinhaus report a case cited by Frank of a woman with syphilis who developed a polydipsia and polyuria. Two months later, the patient had disturbance of vision with hemianopsia. The amount of urine averaged daily from six to seven quarts with a specific gravity of 1.002. After treatment of the syphilis for three weeks, the eye symptoms cleared up and in six weeks the polyuria had ceased. Frank(*c*) also cites two cases of Oppenheim's due to syphilis. The first case exhibited a marked polyuria and polydipsia. Soon after, visual disturbances appeared which later became a complete hemianopsia. The eye symptoms were helped by treatment but the thirst and excessive urination were unchecked. About six months later the patient died. At autopsy a gumma was found in the region of the chiasm. Further back in the region of the optic tract was a growth of more recent date. The second case also exhibited the syndrome of diabetes insipidus and hemianopsia but had no other evidence of brain trouble. The symptoms were promptly relieved by treatment. A few months later the patient died in coma. The autopsy revealed a syphilitic meningitis with a typical gumma in the chiasm extending through the crossing.

Pregnancy.—In pregnancy, the polyuria and thirst may at times be so severe as to suggest diabetes insipidus. Marañon calls attention to the disturbed function of the hypophysis during pregnancy and cites a case, reported by Gentili, of a female, age 40 years, suffering from osteomalacia. At the sixth month of gestation, the symptoms of diabetes insipidus developed and were relieved by the administration of pituitrin. Such evidence must be regarded as more or less doubtful. This is further exemplified in two cases recorded by Nicolaysen. The first was in a woman of 44 years. Symptoms of thirst, polyuria, weakness, and anhidrosis developed gradually after confinement. Temporary relief was obtained by the use of pituitrin. The second case was a woman 34 years of age. The symptoms of thirst and polyuria appeared during the last months of pregnancy. There was no conclusive evidence of pituitary involvement in either of these cases.

During the menopause, symptoms resembling the syndrome of diabetes insipidus may appear. Marañon records two such cases in his monograph.

Symptoms and Signs

The character of the phenomena exhibited by a patient depends on many factors, chief of which are the nature and location of the lesion, age of patient, and time of onset. The symptoms and signs are many and varied. Polyuria, polydipsia, anhidrosis, visual disturbances, and impairment of the sex gland function are among the most important.

The amount of urine passed in twenty-four hours may range from three to forty liters, the volume usually being from five to seven liters. The specific gravity is low and in inverse ratio to the amount voided. It rarely exceeds 1.008 and may be as low as 1.001. Polyuria may be the most striking symptom. A degree of thirst may be present which in most cases is insatiable. Some patients will drink fluids almost constantly and without evident relief. In adult cases, there is frequently a balance between intake and outgo, but in the young oftentimes fluid will be consumed greatly in excess of that voided in the urine. The skin is generally dry and harsh, due to the inaction of the sweat and sebaceous glands. Leucodermia may be present.

In adult cases, the hair in the axillæ and pubes may be very thin or entirely absent. The eyebrows and scalp do not appear to be involved. The beard may be scanty or grow very slowly. These changes in body hair follow rapidly after the onset of the polyuria.

The body temperature is often subnormal, 96 degrees Fahrenheit not being unusual, and the pulse may be slow. The blood pressure may be low except in those cases complicated by cardiorenal disease. In cases in which the sweat glands do not function and their heat regulation action is lost, there may be considerable elevation of body temperature on hot days. Stoermer reported that one of his cases, unable to sweat, on such an occasion had a body heat of 102.9 degrees Fahrenheit.

Somnolence and marked weakness, tiring on slight exertion, are striking symptoms. The patient may be apathetic and disinclined to help himself or coöperate in treatment. Mental depression and melancholia may be evident.

In his early work, Cushing pointed out that patients with hypopituitarism usually had an increased capacity to utilize carbohydrates; and since the syndrome of diabetes insipidus was thought to be due to a deficiency in function of the hypophysis, increased carbohydrate tolerance as determined by the presence of alimentary glycosuria was looked upon as one of the cardinal symptoms. Abrahamson and Climenko question the value of this conclusion believing that the same phenomenon is observed in other morbid states. In the experimental work of Camus and Roussy on dogs, partial or total removal of the pituitary body did not appear to modify the tolerance for carbohydrates, nor cause the appear-

ance of alimentary glycosuria. Injections of extracts of the posterior lobe in these experimental animals were also without effect on the sugar tolerance. It is quite probable that the ability to utilize carbohydrates can be more accurately determined by studying the blood sugar curve after the oral ingestion of a definite amount of sugar as suggested by Hamman and Hirschman, and Janney, than by merely estimating glucosuria.

In Williams' case numerous blood sugar tests were made with the patient on both moderate and excessive carbohydrate diets which included the ingestion of much cane sugar. The range of these tests was always

Figure No. 1 - Glucose Utilization Test on a Case of Diabetes Insipidus.

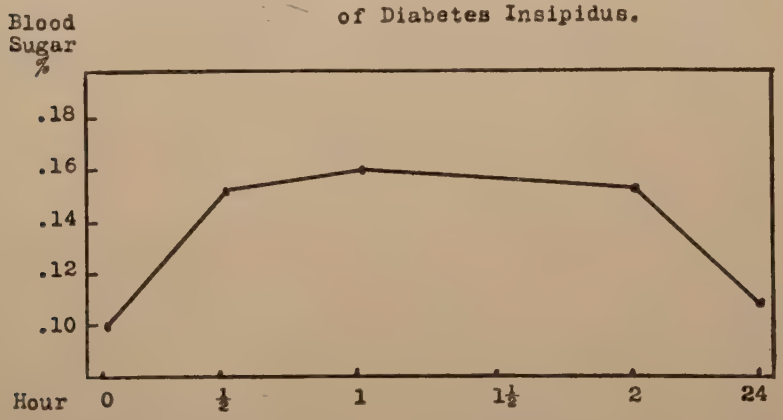

Fig. 1. The patient was given orally, after a night's fast, 107 grams of glucose dissolved in 240 c.c. of water. Samples of blood and urine were taken immediately before the ingestion of the test meal and after at half hour intervals for two hours and at the end of 24 hours. No sugar appeared in the urine. The blood sugar curve is slightly higher than is observed in a normal individual for two hours, suggesting slightly defective utilization, but it returned to normal within 24 hours.

within the normal limits, from 0.08 to 0.11 per cent. A glucose tolerance test performed in this case gave a curve slightly higher than normal (see Figure No. 1), suggesting, if anything, diminished tolerance. There can be no question but that this patient has disturbance of function in the brain areas about the hypophysis, evidenced by the various dystrophies and eye changes present. The constancy and importance of increased carbohydrate tolerance as a symptom of diabetes insipidus may therefore be questioned. It is possible, as Cushing has pointed out, that cases may pass from the hypopituitarism stage to that of hyperpituitarism; or it may be that the hypophysis is not involved as has been suggested by several workers.

The specific gravity of the blood is said to be increased in some cases of diabetes insipidus due chiefly to the accumulation therein of non-colloid salts. The blood of normal individuals varies from 1.040 to 1.065

depending somewhat on a number of factors which include method of test, diet, and age of the individual. A fair average for an adult is 1.055. In a case reported by Strubell in which the thirst was very great, the specific gravity of the blood rose to 1.071. In Williams' case it was 1.052 on a day when 4,000 c.c. of urine was voided.

Ocular disturbances occur very commonly in diabetes insipidus, particularly in those cases where there is tumor formation, injury, or any other cause which produces pressure on the optic chiasm. This brain structure, lying directly in front of the hypophysis, is easily affected when lesions occur in the hypophysis or neighboring brain areas. The eye

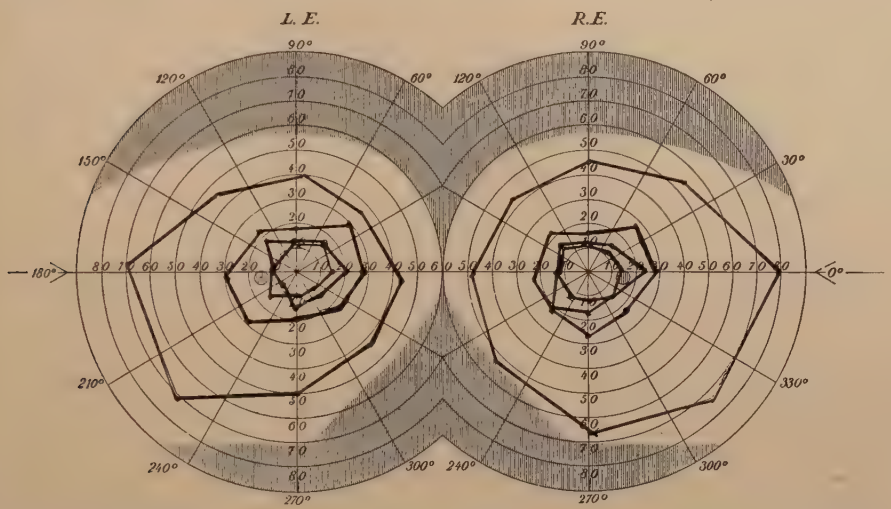

Fig. 2. Case Mrs. W. Severe diabetes insipidus. First observation. Slight concentric contraction of visual fields and well marked contraction of color fields; temporal side most involved.

symptoms which have been observed by different writers are as follows: relative or absolute scotoma; unilateral, bitemporal, or homonymous hemianopsia or hemiachromatopsia. The latter condition is the one which is most commonly seen. In brief, the changes are usually functional and consist in contraction, concentric or quadrantal, of the color fields.

The temporal side often in the upper quadrant, according to Cushing, is most frequently involved. Later the visual or form fields may be involved. In Williams' case at the first examination, there was a very slight concentric contraction of the visual fields and a well marked contraction of the color fields. In the color fields the temporal side was most involved (see Figure No. 2). Five months later, both the visual and color fields were very much contracted (see Figure No. 3). Three and one-half years later the visual and color fields were approximately the same as at the first examination, although in the left eye there was in the lower

temporal a marked quadrantal visual and color defect (see Figure No. 4). If it be true that ocular defects in diabetes insipidus are due to the pressure on the chiasm, in this case the pressure must vary from time to time, indicated by the varying size of the color and visual fields. Continued pressure may cause destruction of some of the optic fibers evidenced by the quadrantal defect in the temporal side of the left eye. Optic neuritis and primary atrophy have been noted by some observers.

Most cases of diabetes insipidus exhibit evidences of perversion of sex gland function or maldevelopment of the genitals. In females, the menstrual function will fail to appear in the young and it will cease in adults.

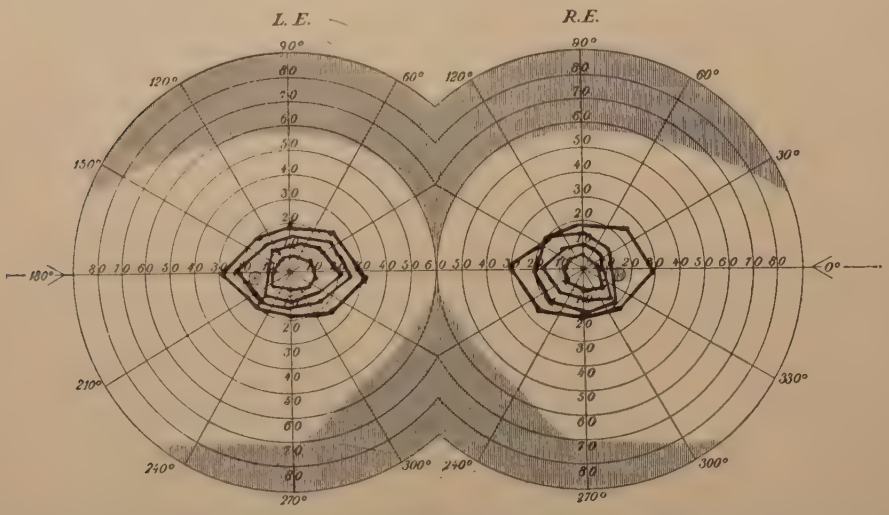

Fig. 3. Case Mrs. W. Second observation five months later. Both visual and color fields are very much contracted.

Males are likely to become impotent. Similarly the genitals in both sexes may remain infantile or become atrophic. Secondary sex characteristics, as pubic hair and the beard, may fail to develop or disappear when present. Such dystrophies as complete or partial giantism and abnormal deposition of body fat may also complicate the syndrome. This phase of the subject is considered in detail elsewhere in this work, accordingly it will not here be further discussed.

Sella Turcica.—Since it has been believed that the hypophysis is involved in the production of diabetes insipidus, clinicians have attempted to gain information as to possible anatomical lesions in this structure by X-ray examination of the sella turcica, because it is this bony cavity which contains the hypophysis. Some writers, particularly Marañon, have attached much importance to the size and shape of the sella as bearing on the question of the lesion in the brain substance which it holds.

In his monograph, Marañon describes in detail seven types of sellæ which are observed in alterations of the hypophysis. He states that it is very difficult to give figures as to the size of the normal sella such as could be measured in the shadow of the radiograph. One therefore has to judge of its normality or abnormality by its size in relation to the dimensions of the individual, by the state of ossification, and form. The following are abnormal types of sellæ: (a) The large form with a wide and deep cavity enlarged in all directions with form of normal shadow, and observed in cases in which congenitally there exists a large hypophysial development. Clinically, there are symptoms of gigantoacromegaly more

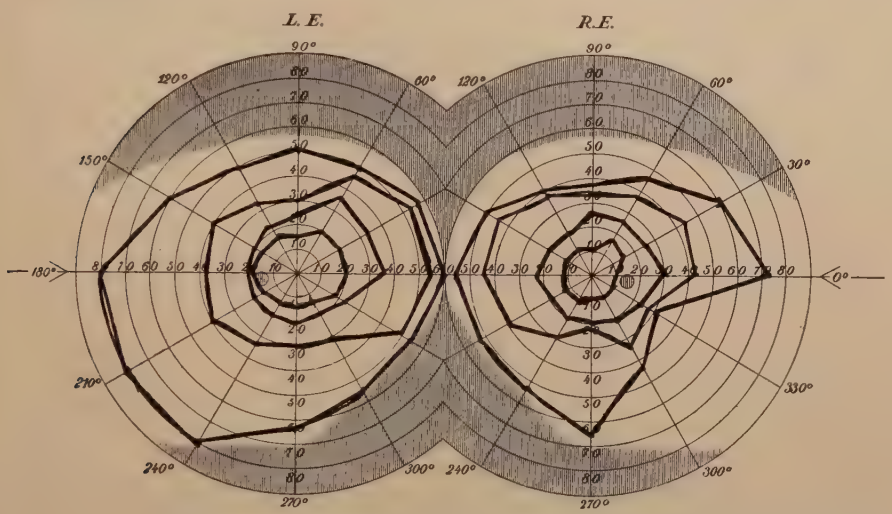

Fig. 4. Case Mrs. W. Third observation three and one-half years later. Visual and color fields approximately same as at first examination, except that in lower temporal field of left eye there is a marked quadrantal visual and color defect.

or less accentuated. In children with hypophysial tumors of rapid growth, this type can be seen, the walls of the sella, being still pliable, widen in all directions. (b) The small sella, which is shallow in depth and narrow in width, but preserving in general the shadow of the normal structure. This type is observed almost always in cases of congenital hypoplasia of the gland (primary hypopituitarism, Cushing). Clinically, this type is seen in cases of infantilism and cachexia. (c) The narrow and deep sella. These cases are almost always due to congenital hypoplasia of the hypophysis, also noted at times in cases of tumors which increase in depth, especially early in life when ossification is not complete. (d) The wide and shallow type. This generally means a developed tumor in the somewhat more advanced stages and which grows upwards destroying the anterior and posterior clinoidal processes. (e) In some cases the entire shadow of the sella and of the sphenoidal processes has disappeared,

being replaced by a confused image. This type is seen in some tumors and especially in inflammatory lesions as meningitis and syphilis which include in their mass the surrounding brain tissue. (f) A less frequent form is one in which the sella is of normal size or smaller than normal. There appears to be a bony bridge binding the anterior with the posterior clinoidal processes. This bony anomaly causes pressure on the infundibulum, the posterior lobe and base of the brain, producing diabetes insipidus.

Cushing attaches value to sellar X-ray examinations, particularly in long standing tumor cases.

In a recent study of the sellæ of one hundred normal individuals by this method, Jewett found quite marked variations in size and shape. The individuals examined represented all ages and variations in weight and stature and these seemed to be factors having to do with the shape of the sellæ. Jewett classified his findings into eight groups which represent nearly every variety observed by Marañon. In the light of present accomplishment, X-ray evidence in the study of the majority of cases of diabetes insipidus must be regarded as of uncertain value.

Pathological Anatomy

As has been indicated, most of the workers in this field, led by Frank and Cushing, have believed that diabetes insipidus is due in most instances to a lesion of the hypophysis. According to Camus and Roussy, this organ has little to do with it. In a series of experiments on dogs, they showed that when the hypophysis alone was injured, polyuria did not result. But when the brain area about the infundibulum, forward to the optic chiasm and posterior to the level of the gray substance in the tuber cinereum, was stimulated or damaged, polyuria promptly followed (see Figures 5 and 6). They state with emphasis that the lesion which determines polyuria in no way concerns the pituitary body. The depth of the injury has nothing to do with the intensity of the polyuria, a superficial lesion being sufficient to produce the phenomenon. In their experiments, the polyuria appeared to precede the thirst and they are definitely of the opinion that the latter is merely a consequence of the former. Leschke also believes that the hypophysis is not concerned in the production of the syndrome and that when a tumor in this organ does cause polyuria, it is because it presses upon the tuber cinereum. In basal meningitis when polyuria is observed, the hypophysis may not be involved. If the pituitary alone is destroyed by disease, polyuria is never observed. Houssay reaches similar conclusions as to the brain areas involved in the production of the syndrome. Cushing, on the other hand, believes that some cases at least occur in pituitary insufficiency, basing his conclusion partly

on the work of Motzfeldt whose experiments indicate that the posterior lobe extract has not the diuretic properties attributed to it by physiologists and on the results of his own surgical experience. He has had a number of cases in which the syndrome of diabetes insipidus has appeared after pituitary operation and in which he thinks other brain areas were not injured. He also has had cases in which it has been possible to remove

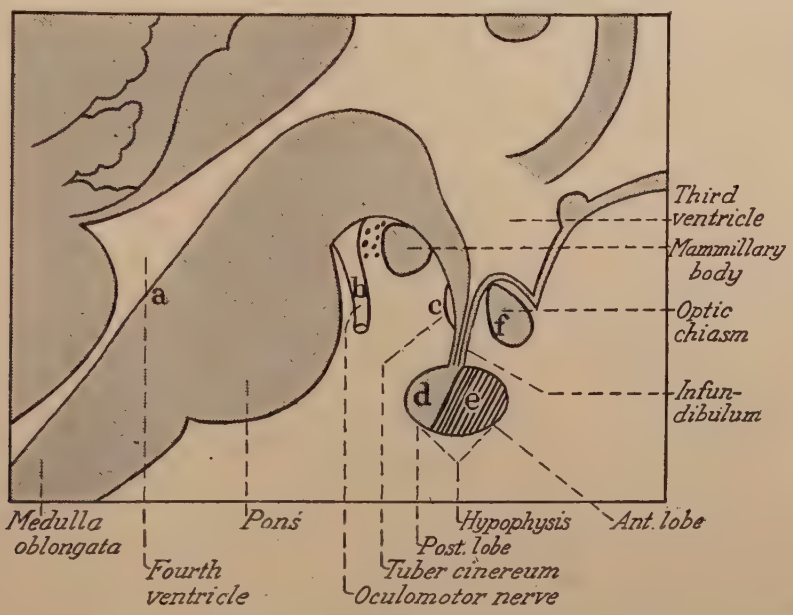

Fig. 5. Diagram of vertical section of brain in region of hypophysis. Lesions at indicated points produce the following physiological and anatomical results:

a. Bernard's piqûire. Glycosuria.
b. Eye palsies and double vision.
c. Polyuria and polydipsia (Camus and Roussy).
d. Polyuria and polydipsia (Cushing, Motzfeldt and others).
e. Dystrophies of body growth, giantism partial or complete; abnormal depositions of fat (Froelich); defective development or disturbance of function of sex glands and secondary sex characteristics.
f. Scotoma, hemianopsia, hemiachromatopsia, primary optic atrophy.

completely suprasellar congenital tumors associated with diabetes insipidus and in which the polyuria subsequently was not modified.

The explanation of extreme thirst and excessive urination in diabetes insipidus was shrouded in much mystery until experimental work on the hypophysis and contiguous brain areas made clear that the disturbed function was purely a secondary phenomenon. Finkelenberg expressed the opinion that there are cases of primary polyuria with organic brain disease in which the ability of the kidneys to concentrate urine is not disturbed to any degree. In such cases there is a noticeable dependence of the quantity of urine upon the character of the food which acts as an abnormal

stimulant to the kidneys. He stated that the power to concentrate urine does not decline in patients who suffer with the disease for years. Ebstein (*g*) was of the opinion that the disease is of nervous origin and that polyuria is a consequence of thirst. Meyer(*b*) concluded that the polyuria was due to a lack of power of the kidney to concentrate urine. Fitz studied by the newer methods of investigation the problem of kidney function in his case and concluded that there existed a hyposthenuria due to the hypersensitiveness of the renal vessels and that polyuria resulted from the diuretic

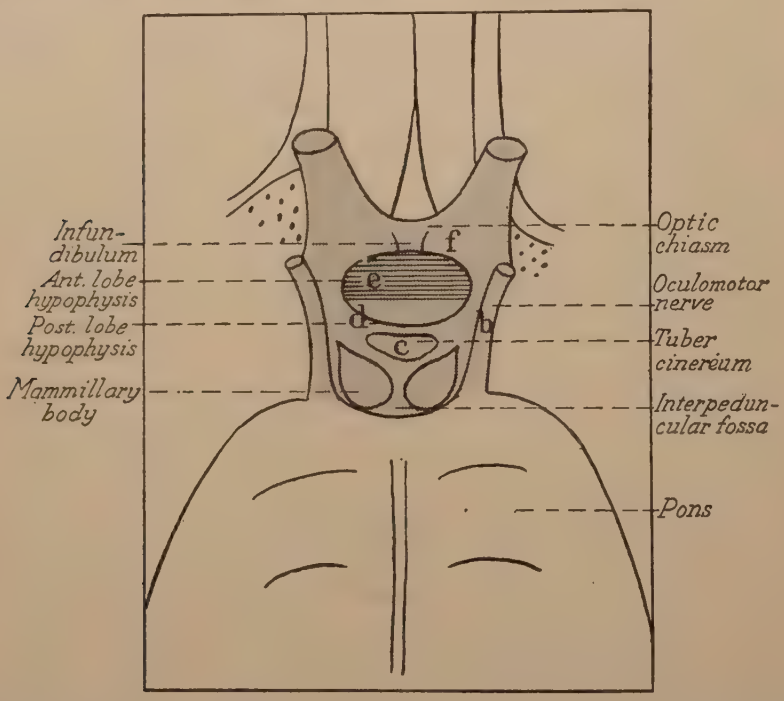

Fig. 6. Diagram of ventral surface of brain in region of hypophysis. Shaded area shows portion of brain involved in the production of the clinical syndromes of disturbed vision, acromegaly and giantism, dystrophie adiposogenitalis and diabetes insipidus, as indicated by the legend of Fig. 5.

properties of the sodium chlorid. The concentrating power of the kidney was not entirely lost. Meyer, Fitz(*d*), and Leschke have shown that when extra salt or urea is added to the diet, they are eliminated in the urine. They are concentrated to a greater degree in the urine but more water is needed to eliminate them. Other salts by way of compensation are concentrated to a lesser degree. Polyuria, therefore, is a result of ingested salt and an inability of the kidneys to concentrate it to any amount in the urine. In this connection it would be interesting to know the relative proportion of sodium chlorid to total blood solids. Since the concentration of chlorids in the blood plasma is fairly constant any absolute increase of

chlorids should be attended by a corresponding increase in water and a relative diminution in other solids. Leschke(*c*)(*d*) points out the well known fact that normal kidneys, when water is withdrawn, can concentrate urine to a very high degree, whereas in diabetes insipidus the specific gravity rarely reaches 1.010. When insufficient water is given, symptoms of uremia result, the freezing point of the blood serum falls and the concentration of urea and sodium chlorid in the blood may reach a very high level. He ascribes thirst to a local stimulation of the cortex of the brain by the increased amount of salt in the blood.

Prognosis

The outcome of any case of diabetes insipidus depends entirely upon the nature of the causal lesion. Cases due to tumor are always serious. Whether the course is long or short depends upon the malignity of the growth. Where the syndrome is due to syphilis, the prognosis is relatively not so serious. Much depends upon early and thorough antiluetic treatment. Cases associated with brain injury are often very severe in character and of short duration. In those instances where the symptoms are apparently due to a disturbed function of the hypophysis, the course is light and transitory. This is usually the case in the polyurias of menopause and pregnancy. In many cases, chiefly those of obscure origin, the syndrome may persist for ten to twenty years or even longer. Age seems to make no difference; children may live for years and adults may die quickly, or the converse may be true. In some cases the polyuria disappears to reappear again while other symptoms may persist and become more aggravated. Death usually results for reasons which have nothing to do with diabetes insipidus, being caused by some associated disease. Where the illness has persisted for a long time, cachexia may be very pronounced. As in many brain lesions, coma often precedes death.

Diagnosis

The recognition of the syndrome is comparatively easy. The cardinal signs are severe polyuria, a sugar-free urine of low specific gravity, insatiable thirst, dry skin, and weakness. The diagnosis is confirmed if these are promptly relieved by the subcutaneous administration of pituitrin. Disturbances of vision, sex gland development and function may or may not be present. With this evidence at hand, it may be assumed that there is some lesion or functional disturbance in the brain area between the optic chiasm and the interpeduncular fossa. The nature of this lesion should be carefully investigated. In the absence of history of injury, evidence of gumma, tuberculosis, or brain tumor should be sought.

Differential Diagnosis

Diabetes insipidus is to be distinguished from a number of other diseases which are characterized by polyuria. Chief among these may be mentioned diabetes mellitus, functional neuroses as epilepsy and hysteria, cardiovascular disease in which there may be cardiac hypertrophy, arterial hypertension, and arteriosclerosis. Chronic kidney disease, including pyelitis and amyloid kidney, may also simulate diabetes insipidus. Some individuals from force of habit and those accustomed to drinking large quantities of fluids as milk, beer, cider, and fruit juices, may void urine in large amounts.

As compared with cases of diabetes insipidus, the polyuria of hysterical and epileptic individuals develops more gradually and is much less severe. The functional neurotic individual will have much less thirst and the volume and specific gravity of the urine will be much more variable. Only in borderline cases is one likely to confuse polyuria of the neuroses with the syndrome of diabetes insipidus.

In cardiovascular disease, thirst is a minor and usually absent symptom. Frequent and increased night urination characterizes chronic nephritis; in diabetes insipidus, the polyuria is constant both day and night. Furthermore, the urine of the nephritic shows definite and characteristic changes which are not observed in uncomplicated cases of diabetes insipidus; as for example, pus, renal cells, casts, and marked variations in specific gravity. The blood of the nephritic usually shows evidence of nitrogen retention as increased urea, creatinin, and uric acid. Edema due to chlorid retention may be present. In pure diabetes insipidus, nitrogen retention and edema are not factors. The body of the cardionephritic does not show the dystrophic changes which are so evident in diabetes insipidus, as very dry skin with absence of perspiration, anhidrosis, and genital maldevelopment. Arterial hypertension and cardiac hypertrophy are not a part of the symptom complex of diabetes insipidus.

Diabetes mellitus is easily distinguished from the insipidus type by the high specific gravity of the urine, glycosuria, increased blood sugar, and frequently complicating acidosis. The distressing symptoms of diabetes mellitus are promptly relieved by proper restriction of diet, but are unaffected by pituitrin administration. Diabetes insipidus cannot be alleviated by diet but is benefited by pituitrin.

Cases of combined diabetes mellitus and insipidus and reports in which the former type has changed to the latter or conversely have from time to time been published. It cannot be assumed that true diabetes mellitus is present unless there is a definite hyperglycemia which bears a more or less direct relation to food intake. Cases of diabetes insipidus which from time to time show traces of urine sugar are more likely to be of the renal

diabetic type, in which the blood sugar is normal or subnormal and in which there is no direct relation between carbohydrate food intake and urine sugar outgo.

The polyurias observed in individuals who overeat or who from habit drink large quantities of fluid are much less severe and easily controlled by restriction of food and fluid intake.

Treatment

Obscure diseases and disease syndromes are characterized by the variety and multiplicity of methods of treatment proposed. To this diabetes insipidus is no exception. Previous to the discovery of the value of pituitary extract as a helpful therapeutic measure, the most commonly used remedial agents were such sedative drugs as the bromids, valerian, opium derivatives, and asafetida. Hydrotherapy and electrical treatment are of no benefit. In cases known to be due to syphilis, antiluetic treatment is indicated. Psychic treatment or the forced restriction of water has not proven efficacious. Thyroid extract has no effect upon the polyuria. In cases associated with brain injury, the endeavor has been made to give relief by spinal puncture and by cerebral operation.

Lumbar puncture has been tried by a number of workers in cases due to other causes than injury but without benefit. Herrick first suggested it as a therapeutic measure. In his case, occasional doses of pituitrin were also given hypodermatically, thus vitiating the value of the test. Furthermore, the symptoms of thirst and polyuria returned very soon thereafter. Fitz's case was not relieved by this measure. In Williams' case, after lumbar puncture, the average daily output of urine dropped from 6,000 c.c. to 3,600 c.c. for one day only. Marañon observed similar transitory effects from its use in two cases. It may be said therefore that the procedure gives only temporary relief due possibly to the lowering of intracranial pressure. The benefit afforded is too fleeting to make the method worth while.

The most useful remedial agent thus far discovered is the extract prepared from the posterior lobe of the hypophysis, familiarly known as pituitrin. To be effective, the extract must be given hypodermatically. The dose recommended by most writers is one cubic centimeter daily. Intravenous injection is inadvisable and not without danger. Within a few minutes after its subcutaneous administration, patients sometimes complain of ringing in the ears, dizziness, or headache. These symptoms, however, soon pass away, as does also the intense craving for water. For the following eighteen to twenty-four hours, the patient will have a feeling of well being and comfort due to the cessation of the extreme thirst and excessive urination. Toward the end of the twenty-four hour period, the

symptoms begin to return and the treatment must be repeated if further relief is to be had.

The daily use of the hypodermic syringe as a means of medication is not without obvious difficulties and dangers. In hospital practice, the method is simple, but in the home it may be necessary to instruct a member of the family of the patient in the technique of the procedure.

To be helpful, the treatment must be repeated daily and indefinitely. The effects of long continued use of pituitrin are unknown. Williams' case was given daily injections for more than a year and then at intervals of a few days for several more months. At the end of that time, the sensation of severe thirst had disappeared and the amount of urine voided daily had decreased one half. The patient, without further treatment, has remained free from thirst for more than one year, but exhibits to a lesser degree the other signs and symptoms which were formerly present, as weakness, eye disturbance, and headache.

The administration of the commercial extract by mouth is without value. Motzfeldt obtained fresh glands daily from an abattoir and fed one patient intermittently from two to seven of these at night with apparent benefit. After two years' treatment, one fresh gland had the same effect as seven formerly did.

Christie and Stewart studied experimentally the action of pituitrin in diabetes insipidus. It is their conclusion that the conductivity of the blood serum is slightly increased and the relative volume of the serum slightly diminished when water excretion is lessened by the extract or by restriction of fluid intake. Blood flow in the hands seems to be increased during the antidiuretic action of the extract, supporting the view that a vascular effect in the opposite direction on the renal vessels may be responsible for diminution in the urine secretion.

Williams studied the clinical effect of pituitrin administration on

	No Pituitrin Administered	1 c.c. Pituitrin Administered Per Hypo
Fluid intake from 7 A.M. to 9 P.M.	3330 c.c.	2280 c.c.
Fluid intake from 9 P.M. to 7 A.M.	2040 c.c.	0
Total fluid intake	5370 c.c.	2280 c.c.
Urine voided from 7 A.M to 9 P.M.	2250 c.c.	1215 c.c.
Urine voided from 9 P.M. to 7 A.M.	3150 c.c.	3110 c.c.
Total urine voided	5400 c.c.	4325 c.c.
Range of amount of urine voided in two-hour periods	100-550 c.c.	44-300 c.c.
Range of specific gravity	1.006-1.009	1.007-1.025
Range of nitrogen concentration	0.15-0.39%	0.21-1.26%
Range of sodium chlorid concentration	0.02-0.12%	0.10-0.94%
Nitrogen eliminated in 24 hours	11.3 grams	12.86 grams
Sodium chlorid eliminated in 24 hours	3.23 grams	6.24 grams

Curves of Two Hour Renal Studies on a Case of Diabetes Insipidus Showing the Concentration of Total Solids, Nitrogen, and Chlorids before and after the Injection of Pituitrin

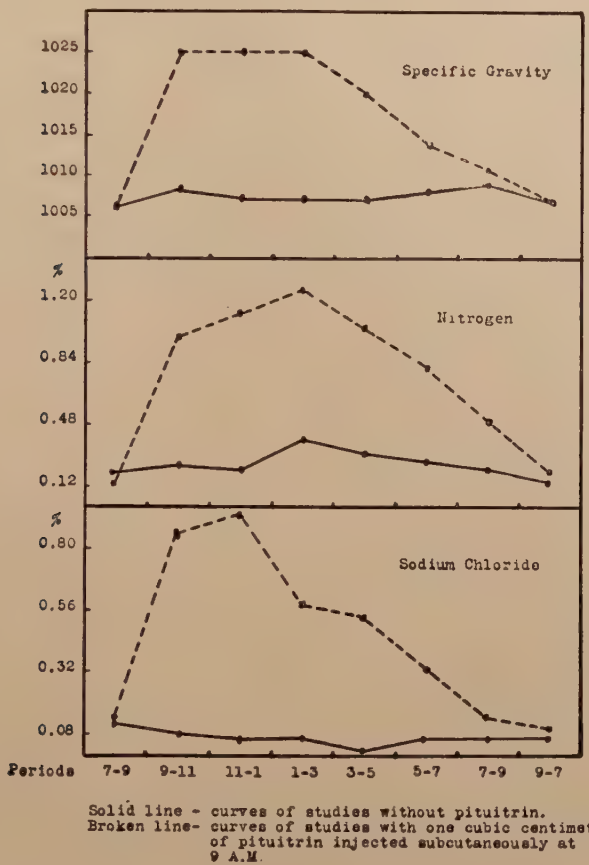

Fig. 7. It will be observed that on the day when pituitrin was not given, the specific gravity of the urine during the various two hour periods ranged from 1.006 to 1.008. On the days when pituitrin was used, during the second period, it rose to 1.025 and there persisted for the next two periods after which it gradually began to fall, reaching 1.007 on the following morning. The per cent of nitrogen followed a similar course. On the day when no pituitrin was given, its range of concentration was from 0.15 to 0.39 per cent; while on the day pituitrin was given, the range was from 0.13 to 1.26 per cent. After the third two hour period, it began to fall gradually, reaching the low level by the next morning. The concentration of chlorids estimated as sodium chlorid gave similar curves. In brief, without pituitrin there is marked fixation of specific gravity and nitrogen and sodium chlorid concentration. Pituitrin enables the kidneys to concentrate for fifteen to twenty hours at a normal rate total solids, particularly nitrogen and sodium chlorid.

kidney function in his case, using the two-hour renal method of Mosenthal. While on a test diet containing approximately 85 grams of protein and 5 grams of added salt, two-hour renal studies were made with and without pituitrin administration. The day period in each test began at 7 A. M.

and ended at 9 P. M., the night period began at 9 P. M., ending at 7 o'clock the next morning. The patient was allowed to drink water as desired. The following is a summary of the important facts observed in the two tests.

A study of the table on page 878 and the accompanying curves, Figure 7, indicates clearly the following conclusions.

1. Before the administration of pituitrin, the patient had a very severe thirst throughout the entire 24 hours. After its administration, thirst was noticeably less, no water being taken during the night.

2. Before pituitrin administration, large quantities of urine of low specific gravity were voided every two hours during the day. After its administration, small amounts of high specific gravity were passed. In both tests a large amount of urine of low specific gravity was voided during the night.

3. Before pituitrin administration, the nitrogen concentration in the urine was very small and quite uniform; after pituitrin, the concentration was much higher and more variable.

4. Before pituitrin administration, the sodium chlorid concentration in the urine was also very small and fixed; after, the concentration was much greater and more variable. On the same diet, almost twice as much of this salt was eliminated before as after the use of pituitrin.

5. The action of the pituitrin is most intense immediately after administration and progressively declines so that by the end of the 24 hour period its action has disappeared.

The Metabolism in Scurvy . . . . . *Alfred F. Hess*

Historical—Chemical Examination of Blood—Studies of Metabolism of Animals—Nitrogen Metabolism in Men and Animals—Summary.

Metabolism in Scurvy

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Studies of the chemical exchanges in scurvy have been surprisingly few. It is a field that should repay investigation, promising to afford a clearer insight into the intermediary metabolism in this disorder. One of the first to touch upon this question was Garrod, who in 1848 reported that there was a diminution of potassium salts in the urine and in the blood of scorbutic patients. In 1877 Ralfe confirmed the potassium deficiency in the urine, but denied its importance from an etiologic standpoint, as he was unable to benefit these patients by administering potassium nitrate. He reported an increase of uric acid in the urine, a diminution of the total acidity, and a reduction of the alkaline phosphates. Litten found the analyses of the urine very contradictory in respect to potassium, but stated that beyond a doubt its uric acid content is increased at the height of the disease, although this diminishes rapidly with convalescence. These few and scattered articles comprise the sum of metabolic studies up to the last decade, and even during the succeeding period they have been very few—so few, indeed, that they furnish insufficient data from which to draw conclusions.

The first careful study of the mineral metabolism in a case of scurvy is that of Baumann and Howard, published in 1912. Its conclusions are not very definite. They may be summed up by their statement that "chlorin and sodium were retained during the fruit juice period, but excreted in excess of the intake during the preliminary period," and that "more potassium, calcium and magnesium were retained during the fruit juice period."

This same year Lust and Klocman published the first metabolism study of a case of infantile scurvy. The baby was eighteen months old, and the metabolic changes were investigated during the active, the convalescent, and "the healing stage" of the disorder. This study seems to have been carefully carried out. The fact, however, that the infant received 800 c.c. daily of slightly boiled milk during the active stage, and was improving at this time, may also have had a beneficial effect on the metabolism in respect to scurvy. The results of these writers are sur-

prising—quite different from what they expected, or what we should have expected. They write: "The balance of the mineral metabolism, including the total ash, the calcium, phosphorus and chlorin during the florid stage of the disease must be regarded not only as not damaged, compared to that of the healthy child, but indeed as somewhat increased." "All the more striking, on the contrary, are the results found during the stage of convalescence. Here the balances were all markedly negative, and only after a lapse of weeks was the tendency manifested to a return to normal conditions." The authors regard these results as indicating a sort of washing out of "dead material" during convalescence—of material which had gathered during the florid stage of the disease. According to their interpretation the disease is due not to a primary or secondary salt deficiency, but to a disturbance in salt elimination, and in the first place of a calcium excretion. This is shown by the fact that even in the "stage of healing," when the total ash and the phosphorus balance once more had become positive, the calcium balance nevertheless remained somewhat negative. The metabolism of infantile scurvy, they believe, far from showing a resemblance to rickets, manifests quite the contrary tendency. The study of this case of infantile scurvy, and that of Baumann and Howard of a case of adult scurvy, comprises the total investigation of the metabolism in human scurvy.

In the course of a recent discussion on rickets before the Medical Society of Vienna, Moll(*b*) stated briefly that in a case of infantile scurvy, at the height of the disease, he found a positive calcium balance which became poor and later negative on giving fruit juice; in other words, a partial confirmation of the work which has just been cited.

In 1913 Bahrdt and Edelstein reported the analyses of the organs of an infant almost nine months old who died of scurvy. An examination of the tissues, especially of the bones, should be especially valuable in checking up determinations of the metabolism during life. This investigation runs absolutely counter to that of Lust and Klocman. The bones showed a decrease of ash, especially of calcium and of phosphorus, and also a lack of calcium in the muscles, but normal amounts in the liver and in the kidneys. These conditions resemble the deficiency of ash and of lime commonly associated with rickets, and it seems quite possible that this infant had rickets as well as scurvy, and that in this way the discrepancy between the two reports is to be explained. The fact that the water content of the bones was two to three times the normal also lends emphasis to this interpretation. *In any metabolism study of infantile scurvy great care will have to be exercised that the disorder is not complicated by rickets,* and the issue thereby confused. It will be very difficult to avoid this pitfall, for there is no test by which early rickets can be diagnosed. The danger of this complication may be realized when we bear in mind that the majority of infants have rickets to some degree. An in-

vestigation of the chemistry of adult scurvy has an advantage from this point of view.

Chemical examination of the blood has yielded such valuable information regarding metabolic diseases that it might be expected to shed light on the disturbances of scurvy. The only investigation from this standpoint is that of Hess and Killian, who have reported estimations of the urea, creatinin, sugar, CO_2 combining power, diastase, cholesterol, chlorin and calcium.[1] The urea content was normal, varying between 12 and 14 mg. per 100 c.c. of blood; this is the average of twenty-one tests on ten cases of infantile scurvy. (In severe cases of beriberi Yano and Nemoti have recently reported that the blood contains an increase of urea, and that its excretion is frequently disturbed.) The creatinin was estimated in two cases and was found to be 2.0 mg. and 1.7 mg. per cent respectively—also normal figures. The blood sugar varied from 0.12 to 0.14 per cent, and was examined in almost all the cases in which urea was estimated; these figures are at the upper level of normality (no attention was paid to the interval elapsing between the feeding and the withdrawal of the blood). The diastatic activity was likewise normal. The CO_2 combining power showed figures under 40 to 45, according to the Van Slyke method, and indicated therefore a mild degree of acidosis. In six cases the chlorids were estimated, the figures being remarkably constant at about 0.42 or 0.43. Cholesterol was a little below normal in the four cases examined. Contradictory results were obtained in regard to calcium. Earlier tests showed a definite deficiency of this salt, but those carried out more recently have generally yielded normal results. Further studies of the blood calcium are highly desirable to ascertain whether it varies in amount in the circulation and especially in different stages of the disease. This aspect is worthy of particular attention in view of the positive calcium balance noted by Lust and Klocman during the active stage of scurvy, and the negative balance during the period of convalescence.

It is evident from the limited data concerning the blood chemistry of scurvy that it is a field which has been inadequately explored and will repay more intensive study. Investigations of this kind have recently been made possible by the introduction of accurate methods requiring only small quantities of blood.

Studies of the metabolism of animals suffering from scurvy are almost as few as those on man. The work of Morgan and Beger, which is frequently quoted in this connection, is not applicable, as it concerns rabbits, which do not develop scurvy. They found that rabbits fed solely on oats and water suffered in their nutrition (loss of appetite, emaciation, paralysis of hind legs), and could be cured by the addition of sodium bicarbonate to the dietary. In 1916 Lewis and Karr published a paper

[1] Almost all of these cases were receiving liberal daily amounts of cod liver oil, which should exclude the possibility of complicating rickets.

on the constituents of the blood and the tissues of guinea pigs fed on an exclusive oat diet. They found the urea content several times greater than normal, but that it fell to normal once more if cabbage or orange juice were given. From the standpoint of scurvy, this investigation is open to the criticism that the diet was too incomplete, and also, as the authors suggest, that the animals suffered from partial starvation and a lack of water.

In the following year Karr and Lewis published a paper on a different phase of this subject, and came to the following conclusions: "No changes in urinary elimination of phenols, nor in the degree of conjugation of the phenols, were observed, provided the factor of partial starvation was ruled out. This is believed to indicate that no increased bacterial action occurs in the intestine of scorbutic guinea pigs, despite the difficulty of evacuation of the feces." These results are in harmony with the bacteriological study of Torrey and Hess, who found that there was no increase in the proteolytic flora of the intestine in infants, or in guinea pigs suffering from scurvy.

In 1917 Baumann and Howard published the only metabolism study which has been carried out on guinea pigs suffering from scurvy, and they are of the opinion that this disorder has a profound effect on the mineral metabolism of this animal. The calcium was excreted in notably large amount; potassium was also lost, and to a greater extent than sodium; the only element which was consistently retained during the active stage, as well as during the period of recovery, was magnesium. This study was followed shortly by one from the same laboratory by Howard and Ingvaldsen, carried out on a monkey suffering from scurvy. It was inconclusive, not conforming to the experiments on the guinea pigs; the authors state that the "changes in the mineral excretion of the monkey during the scorbutic period were not sufficiently significant to admit of easy interpretation." "The marked loss of the various mineral substances encountered in experiments with man and guinea pig was not observed in the present series." It should be remembered, however, that the diets of the guinea pigs and the monkeys were quite different, the former consisting mainly of oats, and the latter of condensed milk. It is quite possible that the basic diet may play a rôle in the metabolism of this disease, although, as stated elsewhere, its effect cannot be noted clinically. Special attention should be paid to this factor in metabolic studies, in view of the widely held opinion that the carbohydrates exert a potent influence in the development of beriberi.

The investigations of the nitrogen metabolism in scurvy in man and in animals have been most unsatisfactory. The two on human beings—an infant and an adult—were negative; that on guinea pig scurvy cannot be utilized on account of the restricted diet of oats, which contained insufficient nitrogen, whereas the one on the monkey showed some loss of nitro-

gen, which led the authors to suggest an increased nitrogenous catabolism in scurvy. This comprises the total data on this subject.

Summarizing the results of these few metabolic studies, it may be stated that they harmonize in respect to only one point—the positive balance of calcium during the active stage of the disease. The investigation of Baumann and Howard on adult scurvy, of Lust and Kloeman and of Moll(*b*) on infantile scurvy, and of Howard and Ingvaldsen on the monkey, are all in agreement in this important conclusion.

Diagnosis and Treatment of Beriberi . . . . . *Carl Voegtlin*

Introduction—Pathology—Symptomatology—Treatment.

Diagnosis and Treatment of Beriberi

CARL VOEGTLIN

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Introduction.—Beriberi is an acute or chronic, endemic or epidemic disease most prevalent among the rice-eating population of Japan, Dutch Indies, the Malay States, the Philippines and certain parts of China and India. It has also been observed in Central and South America, Africa and North America. In 1890 Putnam and Birch reported a number of cases among New England fisherman. The first American epidemic was reported by Bondurant (1895-96) from the State Insane Asylum at Tuscaloosa, Alabama. The disease was also recognized in 1895 at the Arkansas State Insane Hospital and in 1907 at the Texas Lunatic Asylum. In 1912 Little reported an epidemic of beriberi among the inhabitants in Labrador and Newfoundland who, during the winter season, had lived largely on white bread.

Beriberi is now generally considered as a disease due to the continued consumption of food deficient in antineuritic vitamin (water-soluble B), and therefore belongs to the group of deficiency diseases. The dietary theory of the origin of the disease is supported by numerous epidemiological observations which clearly show that the disease is apt to occur when the diet is restricted to highly milled (white) rice, corn or patent flour, whereas it does not appear if less highly milled cereal foods form the bulk of the diet. In this connection, it may suffice here to refer to the important experiments on the production and prevention of beriberi in man carried out by Fraser and Stanton(*a*)(*b*)(1909), and Strong and Crowell (1912). Fraser and Stanton found that under well-controlled sanitary conditions 20 cases of beriberi occurred among 220 prisoners fed largely on "white" rice, whereas no cases appeared among 273 prisoners on "parboiled" rice. The cessation of the outbreak in the former group followed the substitution of parboiled rice for white rice. Further evidence of the dietary origin of the disease was furnished by the important discovery of Eijkman (1897), who observed in chickens fed exclusively on white rice a disease which he considered to be similar to beriberi. This observation has been confirmed over and over again by numerous investigators, who also showed that pigeons develop the same disease, which on account of its striking nervous manifestations was called *polyneuritis gallinarum*. Deficiency

polyneuritis was also observed in rats by various authors, and Voegtlin and Lake (1919) have shown that it can be produced with great regularity, and with very striking symptoms, in cats fed on beef which is autoclaved for three hours after a sufficient amount of sodium carbonate has been added to render the mixture alkaline to litmus. The final link in the chain of evidence was furnished by Funk,[1] who isolated from rice polishings, and certain other foods which were known to possess preventive properties, a substance which was exceedingly efficient in relieving the symptoms of polyneuritic birds. The probable identity of this substance with so-called water-soluble B was finally established by McCollum and Kennedy (1916) and Drummond(*a*)(1917).

Some writers have regarded polyneuritis gallinarum as a condition resulting from starvation. To this may be replied that polyneuritis appears even in animals under forced feeding (Chamberlain, Bloombergh and Kilbourne, 1911).

Pathology.—The principal characteristics of the pathological anatomy of this disease include: (1) degenerative changes in the nervous system; (2) changes in the heart; and (3) anasarca and effusions in various parts of the body. In acute cases, the body may be in a fair state of nutrition, in chronic cases extreme emaciation is found. In acute cases there is also some edema, which at times may be excessive, involving the legs and face. The lungs may be congested and edematous. The right heart is always greatly dilated in acute cases and often hypertrophied in chronic cases. Microscopically the myocardium shows more or less loss of striation of its fibers, which are vacuolated. There is an increase in pericardial fluid. The mucosa of the stomach and upper intestine is hyperemic and more or less injected. The liver and the tubular epithelium of the kidney show cloudy swelling and fatty degeneration. The fibers of the skeletal muscles have an indistinct outline, and the sarcoplasm is swollen or separated from the sarcolemma. Baelz (1882) was the first to call attention to the existence of a peripheral neuritis in beriberi. This was confirmed by Scheube (1884) and others. The peripheral nerves show a varying grade of hyaline degeneration. Kagoshima (1918) observed atrophy of the optic nerve in four out of 50 autopsies. Dürk (1908) and Wright (1905) describe the occurrence of degenerative changes in the spinal cord. The meninges and brain may be hyperemic, and the fluid in the ventricles is often found increased. Acute degeneration of the vagal ganglia at the base of the fourth ventricle has been observed. Recently Shimbo (1918) examined the adrenals in 19 cases of beriberi and found hyperemia and hypertrophy of the cortex without degeneration; the medulla was also hypertrophied with marked round-celled infiltration around the vessels. According to Ono (1916) the epinephrin content of the adrenals is increased.

[1] See chapter on metabolism of vitamins.

The pathological changes just mentioned have also been observed in *experimental polyneuritis,* although the edema, so pronounced in certain human cases, is only of moderate intensity and is usually absent in animals. Vedder and Clark (1912) conclude from the study of the disease in pigeons that the heart may show no microscopic changes, or may show slight edema and pigmentation, or an appearance of beginning mucoid or parenchymatous degeneration. In marked cases every fiber of the vagus usually shows degenerative changes, but no marked changes suggestive of degeneration were observed in the cervical sympathetic ganglia, or in the post- or preganglionic fibers. Myeline degeneration of the sciatic nerve is a constant finding. Degenerative changes were observed in both dorsal and ventral roots, and in both axic cylinder and medullary sheath in the fibers of all columns of the thoracic spinal cord, also in certain large cells in both ventral and dorsal horns of the gray substance of the lumbosacral cord (Nissl method). No abnormality in mitochondria was noted in the cord. "The symptoms of the disease are not chiefly referable to the degeneration of the peripheral nerves, since the degeneration occurs before symptoms arise, and because advanced degeneration may be present accompanied by no symptoms at all, and because degeneration of the nerves results after recovery has occurred." Funk(*b*)(1912) has analyzed the brains of normal and polyneuritic pigeons and found that the latter showed a decrease in total nitrogen and phosphorus. Funk and Douglas (1914), and Williams and Crowell (1915) have observed degenerative changes in the glands with internal secretion. McCarrison(*a*)(1919) comes to the conclusion that beriberi is not merely a polyneuritis, but that it leads to functional and degenerative changes in every organ and tissue of the body, as evidenced by great atrophy of the skeletal muscles, the reproductive organs, thymus and spleen; the bones are thinned and the marrow is diminished. A mild degree of anemia is present. The adrenals are hypertrophied in all cases where an increased amount of fluid in the pericardial sac was noted, an observation which leads McCarrison(*b*)(1920) to attribute the edema in beriberi to an excessive production of epinephrin. The vitamin deficiency finally renders the body very liable to infection. According to Midorikawa (1918), the blood pressure is not increased in beriberi, although the hypertrophy of the adrenals is very marked at autopsy.

In the chapter on the metabolism of vitamins, it was stated that Funk, Braddon and Cooper and others have claimed a relationship between the antineuritic vitamin and carbohydrate metabolism. Thus it was found by Funk(*d*)(1914) that an increased consumption of carbohydrate-rich foods hastens the onset of polyneuritis. Funk and Schönborn (1914) then showed that in polyneuritis gallinarum, the glycogen almost completely disappears from the liver and there is present a marked hyperglycemia, both of which conditions return toward the normal on

the addition of vitamin to the diet. The blood sugar of beriberi patients was found increased (Suga, 1919, and Suzuki(*a*), 1916) in severe, acute cases. Yoshikawa, Jano and Nemota (1917) observed an increase in urea in the blood in severe but not in mild cases of beriberi, and the refractive index of the blood serum was found normal. Nursing infants, suffering from beriberi, were shown by Suzuki(*b*)(1917) to secrete an increased amount of amino-acid nitrogen in the urine, an observation which this author attributes to abnormalities in the intermediate protein metabolism resulting from impaired liver function. Aron and Hocson (1910) studied the metabolism of a beriberi patient in a fairly advanced stage of the disease and observed that the utilization of nitrogen and phosphorus is reduced. Ramoino (1916) studied the respiratory metabolism in pigeons on a polished rice diet and noted that the respiratory quotient is lowered. The quantity of oxygen consumed does not follow a descending curve parallel to that of the carbon dioxid excreted. The addition of rice polishings to the diet is followed by a prompt return of the respiratory quotient to normal. Drummond(*b*)(1918) found a marked creatinuria in rats fed on a diet deficient in antineuritic vitamin, a fact which is probably explained by the marked wasting of muscle tissue under these conditions. Dutcher and Collatz (1918) found the catalase activity of the blood and tissues reduced in polyneuritis.

Symptomatology.—Clinically the disease has been divided into various types. It should be remembered, however, that these various types are manifestations of one and the same morbid process, and that one form may suddenly pass over into another form. Perhaps the most useful classification is that which recognizes the so-called "wet" and "dry" beriberi, these two types being distinguished chiefly by the presence or absence of edema. The period of development of beriberi has been estimated by Fraser and Stanton (1908) as at least 80-90 days. The onset is usually gradual, the patient complaining for some time of malaise, heaviness, numbness and weakness of the legs. Other complaints are loss of appetite, constipation, palpitation and dyspnea after moderate exertion, pain caused by deep pressure on the muscles of the legs. As the disease progresses, certain objective symptoms can be made out, such as edema over the tibia, slight hyperesthesia over the internal surface of the lower extremities, increase or decrease of the knee reflexes, increased pulse rate and heart action. Kato and Yamada (1918) examined two cases of beriberi and found no evidence of cardiac irregularity until the patients were convalescing, when a slowing of the pulse was noted, and the electrocardiagram showed a condition of sinusarythemia. This they attribute to vagotonia, as atropin relieved the arythemia. Enlargement of the heart can be readily demonstrated by percussion, and the downward and outward displacement of the apex-beat. Systolic heart murmurs may be present and the second heart sound over the pulmonic area is particularly

accentuated and sharp, and may be reduplicated. These changes are not due to stenosis or insufficiency of the valves as shown by post mortem examination.

The body temperature is usually normal, but slight fever has been observed in some cases. The right heart dilates, and on account of insufficient heart action the urine is diminished and the edema rapidly increases. Sometimes effusions into the pericardium, pleura and peritoneum occur. Marked motor disturbances now manifest themselves, first in the gait of the patient, which is generally of the "high-stepping" type, the foot being raised with difficulty, brought forward with a jerk and lowered abruptly. There is a tendency to walk with the legs spread apart. The sensory abnormalities increase in severity and the patient complains of cramps, burning, and the sensation of pins and needles, this being especially noticeable in the anterior tibial and peroneal muscles. The paralysis may extend in severe cases to the abdomen, diaphragm, the intercostals, and also to the arms so as to produce wrist drop, and sometimes complete loss of motor control of the upper extremities. In chronic cases this paralysis leads to extreme muscular atrophy which, however, at first glance may not be easily recognized on account of the coexistence of edema. There may be anesthesia and paresthesia with loss of sense for heat, cold and pain. Little has drawn attention to the presence of night-blindness in beriberi. Aphonia is also sometimes observed, especially in infants, and is probably caused by the paralysis of the muscles of the larynx, which are supplied by the pneumogastric nerve. Painful cramps of certain muscles are not uncommon in marked cases, and fibrillary muscular twitchings and tonic convulsions are sometimes seen in the advanced stages of the disease. Spasticity has been noted during convalescence by numerous observers, causing a gait similar to that characteristic of spastic spinal paralysis.

Voegtlin and Lake (1919) have described similar motor disturbances in polyneuritic cats. In polyneuritis gallinarum the principal symptoms consist of a progressive paralysis of the legs and wings which in the early stages is recognized by unsteadiness of the gait and inability of the birds to roost and fly. A convulsive type is frequently seen which some writers attribute to cerebellar lesions (Richter, 1913); others explain the convulsions by assuming the existence of an unequal degeneration of the nerves innervating flexor and extensor muscle groups.

Diagnosis.—The diagnosis depends largely on the symptoms of peripheral neuritis, the cardiac insufficiency and the generalized tendency to edema, the absence of fever and marked albuminuria. Several other diseases have to be distinguished from beriberi, such as the various common peripheral neuritides caused by alcohol, arsenic, lead and malaria. Alcoholic neuritis may be ruled out by the history, arsenic poisoning by the absence of abdominal pains and diarrhea, lead poisoning by the

absence of colic and the blue line on the gums. Heart disease is eliminated by the absence of the signs of valvular disease, and the presence of paralysis. The differential diagnosis should furthermore take into consideration myelitis, locomotor ataxia, pellagra, kidney disease, and lathyrism.

The opinion generally prevails that beriberi is very rarely found in this country, and while this is undoubtedly true, it should be remembered that the diagnosis of mild cases is exceedingly difficult on account of the vague symptoms which are not at all specific of this disease. Some time ago the writer called attention to the possibility that in the United States incipient cases of beriberi may escape recognition, a view which now seems to be confirmed by the marked improvement noted by Eddy and others following the administration of antineuritic vitamin to infants suffering from "malnutrition."

Treatment.—It is obviously far more important to prevent beriberi by means of a proper diet than to cure it. This can be accomplished by including in the diet a sufficient quantity of foods rich in antineuritic vitamin (see table in chapter on vitamins). The treatment in the early stages of the disease has some chance of immediate success, but the chronic cases require prolonged treatment, and even then some of the anatomical injuries resulting from the disease may never completely disappear. A case of this kind was seen by the writer in a discharged soldier, who had contracted beriberi while on duty in the Philippines. He was discharged from the army and returned to this country, but still suffered from neuritis, which in spite of a mixed nutritious diet had not receded after four years.

Symptomatic treatment is undoubtedly of some value, but since the disease has been shown to be due to a dietary deficiency the main effort should be directed, as will be pointed out later, towards correcting the dietary defect. Acute, cardiac cases should be kept in bed so as to avoid any unnecessary strain on the weakened circulation. This is particularly important, as the fatalities from this type are due to sudden heart failure, which often occurs without a preliminary warning. The heart action may be supported by the use of digitalis and venesection. Hypodermic injections of atropin are advocated by Braddon. Edema and constipation are favorably influenced by the administration of saline cathartics. Bromids tend to relieve the hyperesthesia, and strychnin is used as a general tonic in the treatment of the paralytic symptoms in chronic cases.

The milder cases respond rapidly to a proper change in diet. In adult patients the diet should include green vegetables, legumes, milk and fresh meat, as it has been shown that green vegetables, especially beans and peas, are fairly rich in the antineuritic vitamin.

Specific treatment with vitamin preparations is based on the results obtained in animal experimentation. Soon after the discovery of poly-

neuritis gallinarum, it was shown that aqueous and alcoholic extracts of rice polishings and beans have a marked curative action in polyneuritic birds. A completely paralyzed bird may regain its normal appearance

Fig. 1. Severe polyneuritis due to exclusive diet of polished rice. Complete paralysis of legs. Received intramuscularly 8 mg. vitamin prepared from brewer's yeast.

within a few hours after a few cubic centimeters of an active extract has been administered. Funk has seen similar improvement with 20 mg. of a purified preparation, and Voegtlin and Lake (1919) noted just as striking relief in symptoms in polyneuritic cats. While the effect of the extract

Fig. 2. Same pigeon as in Fig. 1, two hours after injection of vitamin.

in the human is not quite so astonishingly rapid, improvement in patients may be noticed within a very short time. Thus, Chamberlain and Vedder (1912) obtained very satisfactory results with crude extracts of rice polishings in the treatment of breast-fed infants suffering from beriberi.

The infants received 20 drops of the extract (the equivalent of 83 gm. of rice polishings) every two hours. "Improvement was immediate. The vomiting stops in 24-36 hours. The child, who has not passed any urine

Fig. 3. Severe polyneuritis. Spastic type. Received intramuscularly 4 mg. vitamin prepared from brewer's yeast.

in several days, urinates five or six times freely. The edema disappears in the course of a few days. Usually on the first night after treatment is begun the infant falls into a deep sleep, although it may have been practically sleepless for several weeks. The dyspnea and palpitation cease

Fig. 4. Same pigeon as illustrated by Fig. 3, three hours after treatment. (The author is indebted to Dr. Casimir Funk for permission to reproduce these illustrations.)

after two or three days. At the end of a week, or less time, the patients are completely cured with the exception of the aphonia." This symptom finally disappears after about two months of treatment. Similar results were obtained in adult patients by Williams and Saleeby (1915) and by

Vedder and Williams (1913), who used Funk's vitamin fraction and found that the paralytic symptoms of dry beriberi showed immediate improvement.

Excellent results have also been obtained with yeast preparations. Funk and Schaumann have shown that brewers' yeast is probably the richest source of antineuritic vitamin, and Cooper (1914) found that autolyzed yeast possesses marked curative action against avian polyneuritis. Work in the writer's laboratory has furthermore shown that autolyzed yeast treated with some hydrochloric acid will retain its activity almost indefinitely (Myers and Voegtlin, 1920), and that a stable and concentrated preparation can be obtained from autolyzed yeast by treatment with fullers' earth (Seidell, 1915). Autolyzed yeast was tried in the treatment of 45 cases of human beriberi by Saleeby (1919). He reports that the preparation is well tolerated in doses of 15-40 c.c. 3 times daily for adults, and from 2-4 c.c. every 3 hours in breast-fed infants. Marked results were noted in less than 3 days, and a week's treatment seemed to give full relief in mild cases. Edema yielded quickly and the appetite improved at once. Chronic changes in the nerves remained unaffected.

In conclusion, reference is made to the results obtained by Eddy and Roper (1917) in the treatment of marasmic infants with a vitamin preparation made from sheep pancreas. This extract was shown to contain the antineuritic vitamin in relatively large amounts and its administration to the patients was followed by marked improvement in general appearance and resumption of growth. Similar results were reported by Daniels, Byfield and Loughlin (1919), who demonstrated the beneficial action of extracts from wheat embryo, carrots, turnips and celery on the growth of artificially fed infants.

Pellagra . . . . . *Ward J. MacNeal*

Definition—Etiology—Theory of Etiologic Relationship Between Pellagra and Beriberi—Theories of Dietary Deficiency—Geographical Distribution—Social Status—Relation to Food—Sewage as an Etiologic Factor—Pathological Manifestations and Course—Clinical Course—Pathological Anatomy—Pathological Chemistry—Bacteriology—Diagnosis—Prophylaxis—Treatment.

Pellagra

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NEW YORK

Definition

Pellagra is a specific disease of man characterized by clinical signs and symptoms, by geographical location and by seasonal relationships. The clinical features include inflammation of the digestive tract, various grades of toxic nervous disorders, and a peculiar cutaneous eruption which is the most characteristic feature of pellagra. This is a symmetrical erythema which involves especially the backs of the hands and passes regularly through a stage of erythema, a stage of hyperkeratosis, a desquamative stage to restitution with more or less atrophy of the skin. The location, nature and evolution of this eruption has the same importance in the diagnosis of pellagra as has the eruption of measles or of smallpox in the diagnosis of these diseases.

Etiology

Specific Causation.—Roussel in 1866 concluded that pellagra is caused by two groups of factors. One of these, the extrinsic factor, is altered maize, which is the specific cause of pellagra, giving to the disease its character as a disease entity and without which there can be no pellagra. However, there is required in addition certain conditions of vitality within the body of the victim, just as seeds require suitable soil for their development. All causes of enfeeblement create this necessary vital condition of susceptibility. Such, says Roussel, is the dual basis indispensable as a solid foundation for the etiologic theory of pellagra. This view of Roussel contains much that is admirable and still deserving of respectful consideration. For nearly forty years it remained almost unchallenged. Sambon in 1905 launched a most successful attack against this maize theory, and numerous other investigators, following him, have shown that pellagra occurs in those who do not eat maize, the possibility of which was absolutely denied by Roussel. Unfortunately, Sambon coupled with his refutation of the maize theory the conception that pellagra is an infectious disease transmitted by a biting fly of the genus Simulium, a theory which has been unable to withstand later investigation.

The Illinois State Pellagra Commission, in 1911, drew the following conclusions:

(1) According to the weight of evidence pellagra is a disease due to infection with a living microörganism of unknown nature.
(2) A possible location for this infection is in the intestinal tract.
(3) Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease.

This commission recommended an increase in animal protein in the dietaries of the State hospitals and also compulsory notification of all cases of pellagra. The Robert M. Thompson Pellagra Commission, after most extensive epidemiological study of pellagra in the general population of certain pellagrous districts, has come to conclusions supporting the Illinois Commission. Jobling and Peterson(*a*) and their coworkers have also arrived at similar conclusions.

Theory of Etiologic Relationship Between Pellagra and Beriberi.—Sandwith, in 1912, recognized certain analogies between pellagra and beriberi and he suggested that pellagra may be essentially due to a deficiency of nutrition. This theory was taken up with enthusiasm by Funk(*c*), by Goldberger and their followers. The elimination of pellagra from lunatic asylums, prisons, orphanages and other institutional populations by radical improvement in the dietary, as recommended by the Illinois Commission, has been a striking feature of the argument in favor of this deficiency theory. That such results admit of another interpretation was, however, pointed out by the Illinois Commission itself in 1911. In November, 1916, Goldberger and Wheeler claimed to have produced, by the experimental use of a deficient and unbalanced diet, a "typical" eruption justifying a diagnosis of pellagra in six of eleven human subjects. A full report of this work, which appeared after a delay of more than three years, has revealed that the eruption designated as "typical" was actually a dermatitis on the scrotum and apparently on the apposed surfaces of the thighs. Apparently the authors no longer wish to maintain that this is a "typical" eruption justifying the diagnosis of pellagra, for this expression is avoided in the full report. They here even express a doubt as to whether their experimental diet was of the specific quality necessary to cause the usual eruption of pellagra. McCollum(*a*), with his collaborators, has carried out a large series of animal experiments upon diets of the type used by Goldberger and Wheeler, and has finally expressed his conviction that pellagra is an infectious disease.

Theories of Dietary Deficiency.—The deficiency theory has been confronted with a serious dilemma during the period of the World War from 1914 to 1918. Dietary deficiency became the rule in central Europe, and the resulting increase in disease and in death rate has been given wide publicity. Among the diseases increased in this part of Europe during the period of deficient diet, pellagra has been conspicuously absent.

There was observed, however, an outbreak of pellagra among Turkish prisoners in a British prison camp in Egypt. Many of these prisoners were pellagrins before capture, but the disease also actually spread to new victims in the camp. A British Committee of Inquiry ascribed this outbreak to the deficient diet of the Turkish prisoners and contrasted this diet with that of the German prisoners in an adjacent camp. The German prisoners had subsisted upon a most excellent diet before capture, and as prisoners were receiving a diet above reproach. Most unfortunately for the conclusions of this Committee, an outbreak of pellagra appeared among these German prisoners immediately after their diet had been found to be above reproach, namely in December, 1918. Enright, who has reported this outbreak, concludes, "Although I have been unable to advance any satisfactory cause for this mysterious outbreak of pellagra, I do submit that I have established a clear case against a 'food deficiency' as being the only factor involved."

More recently Enright, and after him Stannus, has suggested that perhaps some toxic disturbance of the endocrin glands may explain pellagra. Whether this suggestion will be followed with enthusiasm, similar to that aroused by the deficiency hypothesis suggested by Sandwith eight years previously, only the future can tell.

In my own opinion the causation of pellagra depends upon two factors analogous to those recognized by Roussel: (1) a living microörganism, which is the specific causative factor, without which pellagra does not occur; and (2) a group of factors, quite non-specific, which serve to reduce the resistance of the victim. In this latter group are recognized malnutrition, either from inadequate food or inability to utilize food adequately, cachexia, overwork, depressing influence of hot weather, strain of reproduction in women, involution of old age, alcoholism, and other such influences. The specific causative factor remains unrecognized. Most probably it is a microbe which resides in the gastro-intestinal tract, from which its soluble products are absorbed to give rise to the distant manifestation of pellagra. In regard to transmission of the infectious agent, the weight of evidence indicates that it passes to new victims by contamination of food and drink with intestinal excretions, that it is disseminated only within short distances from cases of the disease, and that it attacks successfully only a small proportion of the exposed population.

Geographical Distribution.—Isolated cases of pellagra are occasionally observed in various parts of the world. Because of the chronic and recurrent character of the disease and the extent of modern travel, such observations are to be expected. However, the relation between place and origin of pellagra is one of the most striking and characteristic features of the disease. Pellagra is contracted where there is a preëxisting case of the disease and its apparent sporadic origin is relatively so rare as to

warrant a grave doubt as to the accuracy of diagnosis or the adequate search for antecedent cases in such instances. Malnutrition and lack of food are conspicuous among the poor of large cities where pellagra is quite unknown, but in pellagrous districts a very large proportion of the poorly nourished and especially the women and children are attacked by pellagra.

Regional Incidence.—Pellagra is prevalent in certain parts of Turkey, Egypt, Roumania, Austrian Tyrol, Northern Italy, West Indies, Yucatan and the Southern United States. It has occurred in South Africa and the Malay States. Within these large areas it occurs in small endemic foci, the great mass of the population being relatively free from the disease. In fact, pellagra is contracted especially by those who actually reside in the same house with pellagrins or next door to such houses.

Race, Age and Sex.—Pellagra is more prevalent in the white race than in negroes in the United States. It is, however, a much more fatal disease in the negro, doubtless because of the lower racial resistance, greater poverty and poorer diet of this race. The great bulk of the cases occur in women and children, but old men are also attacked rather frequently. Men in the age period 15 to 45 years are rarely afflicted with pellagra unless they suffer from some other depressing condition. The death rate is almost nil in children, and most of them recover in a few years. In women the death rate is moderately low, but the tendency to continued recurrence very high. After the age of 50 years the death rate is well above 20 per cent in the first year and recovery is rare.

Social Status.—In Europe pellagra has been recognized as especially prevalent among the peasants. The industrial factory workers and the commercial population of towns and cities have largely escaped it. In general, pellagra has there been associated with extreme poverty. In the United States, social status is less definitely established. Perhaps the nearest approach to a caste is furnished by the colored population of the Southern States, in which greater poverty appears to be correlated with a lesser prevalence of pellagra. In the white population of these States, pellagra is moderately prevalent among the farmers, but far more prevalent in the families of the industrial laborers in the small factory communities, such as those of cotton mills, and in the more insanitary sections of some of the cities of moderate size, such as Charleston, South Carolina, and Nashville, Tennessee. Institutional outbreaks, especially in lunatic asylums and in orphanages, have also received prominent notice in this country. Occasional cases of pellagra are, however, observed in the well-to-do and cultured members of society, as, for example, a physician, a wealthy landed proprietor addicted to alcohol, the sister of a State legislator, an actress, a lecture entertainer, a nurse, a sister of charity, a sister of a prominent physician, a wife of a merchant, a son of a wealthy

lumberman, a veterinary inspector in the Federal service,—examples recorded by the Thompson Pellagra Commission.

Relation to Food.—According to the older theories pellagra is due to the toxic action of maize in the diet, but modern investigations have disproved this conception. Stannus has reported pellagra in prisoners who had eaten no maize for years, and Viswalingham has observed an outbreak of pellagra in the Malay States among Chinese coolies, whose diet consisted largely of rice and contained no maize. The Thompson-McFadden Commission, in 1913, failed to discover any positive correlation between the frequency of use of any single food and the frequency of occurrence of pellagra. At present no student of pellagra appears seriously to maintain that the disease is caused by any single food. There remains, however, the possibility that the excessive use or too exclusive use of certain foods, maize for example, may predispose to the development of the disease or may render the attack more severe.

A second possibility is that the insufficiency of certain dietary elements, rather than the excess of a certain element, may bear an etiological relation to pellagra. The pellagra-preventing value of animal foods, especially milk, emphasized by the Illinois Commission in 1911, and clearly demonstrated by the Thompson-McFadden Commission in 1913, is now generally recognized. Recently even Goldberger and his colleagues of the Public Health Service (1920) seem to have abandoned the advocacy of beans and to have turned to milk, milk products and fresh meat as preventive diet for pellagra. In my own opinion the pellagra-preventing value of these foods is similar to their value in preventing tuberculosis; they improve nutrition and increase the resistance to the specific microbic cause of the disease. Mere lack of animal foods is not the specific cause of pellagra as is attested by the host of strict vegetarians who escape the disease. On the other hand, a relatively brief survey of a pellagrous district reveals pellagrins who have taken milk daily throughout their lives, especially young children, and occasionally one finds adult pellagrins who have eaten meat every day for years.

The third possibility, namely that general insufficiency of food may be the specific cause of pellagra has already been discussed and rejected. Those nations in which belts were shortened during the years from 1914 to 1919 did not suffer from pellagra. There can be no doubt, however, that adequate nutrition is a most important insurance against pellagra in pellagrous districts and a most important factor in bringing about recovery from this disease and that inadequate nutrition predisposes to the development of pellagra in those who are exposed to the essential cause by residence in pellagrous districts.

Sewage as an Etiologic Factor.—Many of the older authors have mentioned the association of poor sanitation with pellagra prevalence. The Thompson-McFadden Commission (1913) and the Thompson Com-

mission (1917) have emphasized the fact that pellagra originates where insanitary surface privies are used and much less frequently where sanitary water-carriage systems of sewage disposal are properly employed. This relationship has been confirmed by the independent work of Jobling and Peterson(*a*).

Experimental Inoculation.—Attempts to produce pellagra by experimental inoculation have, so far, failed in every instance to yield a conclusive positive result.

Pathological Manifestations and Course

Clinical Course.—Pellagra may prove fatal in three to five weeks after onset or it may persist and recur for forty years. For a discussion of the clinical features of the attack and the subsequent course of the disease the reader is referred to the Third Report of the Thompson Pellagra Commission and to the paper of MacNeal (1921).

Pathological Anatomy.—The gross appearance of the cutaneous lesions has been best described by Merk. Histological studies have been made by several authors but there is still lacking a systematic histological study of the various stages in the evolution of the pellagrous eruption. In general the changes in the skin would appear to result from the action of a toxic irritant carried by the blood or lymph, to which the epidermis of the backs of the hands is particularly sensitive.

The nervous lesions have been somewhat more thoroughly studied. In a rapidly fatal case, Singer found the most pronounced changes in the Betz motor ganglion cells of the cerebrum and in the cells of Clarke's column in the cord, coupled with fiber degeneration diffusely scattered throughout the white matter and not particularly abundant in any tract. Perivascular infiltration was lacking, in striking contrast to the pictures seen in syphilis of the central nervous system and in trypanosomiasis. In more chronic cases hyperplasia of glia about the blood vessels and thickening of the vessels themselves are commonly found. The nervous lesions also, like the cutaneous changes, point to the action of a diffusely distributed toxic substance in solution in the blood and lymph.

The lesions of the alimentary tract also vary with the stage of the acute attack and represent only after-effects in the interval between attacks. Most of the descriptions of the pathology have failed to take into account the evolution of the lesions. During life, the hyperemia of the mouth, pharynx and of the rectum are often prominent features of the active attack. Autopsy at this stage nearly always reveals inflammation throughout the intestine, patchy in distribution. The duodenum, lower ileum, caput coli and rectum commonly show the most severe changes. This rather diffuse enteritis tends to heal with scattered small

round ulcers persisting for some time, often seen at autopsy late in an attack. Later these heal and the only persistent sign in the intestine at autopsy may then be the rather diffuse atrophy of the wall. The lesions of the digestive tract are least well understood. Some authors (Roussel) regard them as entirely trophic and dependent upon antecedent changes in the nerves. Others regard them as an expression of direct toxic action on the intestinal wall by the essential poison of pellagra during its absorption. Doubtless the normal intestinal microörganisms also play a part, particularly after ulceration has occurred.

Pathological Chemistry.—Myers and Fine(*a*) found the gastric juice of pellagrins often deficient in hydrochloric acid and not infrequently in pepsin also. As a rule, the feces contain a marked excess of indol and skatol. The urine, during the attack, commonly shows a trace of albumin and a few tube casts and an excess of indican. The amount of indican is manifestly related to the intestinal derangement. In some instances it is present in enormous quantity. Metabolism studies on pellagrins have shown that these patients possess normal ability to utilize the food principles. In fact, in uncomplicated pellagra, the utilization is surprisingly high, when one considers the other evidence of gastro-intestinal derangement.

There is a fairly voluminous literature dealing with chemical analysis of maize and of other food substances, in some instances coupled with the production of disease in animals or in man by the administration of such foods. The extensive and authoritative work of McCollum and the highly dramatic report of Enright, coupled with the absence of pellagra among the poorly nourished peoples during the recent war, have robbed much of this work of its former interest.

It is clear, however, that milk and milk products favor recovery from pellagra and possess some pellagra-preventing power. Whether this value resides in the fat, in the protein or in the lactose and derived lactic acid, or in less definite accessory food factors would appear worthy of investigation, but, inasmuch as the results of any treatment are liable to considerable variation, a considerable series of cases critically tested would be required to shed light upon this question. The beginner is liable to ascribe too much importance to the favorable outcome of the attack of pellagra, when treated by a dietary method, because he is, as a rule, ignorant of the natural tendency for such attacks to terminate in recovery.

Bacteriology.—The work of Tizzoni and his associates, who have isolated from the blood an organism, which they regard as the cause of pellagra, may probably be dismissed as unreliable. The intestinal flora is profoundly altered in pellagra. There is often a large increase in the variety of organisms present in the feces as compared with the normal as well as a disturbance in the numerical relationships of the normal types. Further investigations in this field are much to be desired.

Diagnosis

The diagnosis has to be made by examination of the patient and may be supported by subsequent demonstration of the typical anatomical changes in the tissues. Of the accessory facts, the most important is a history of having lived in a pellagrous district. The dietary history is of considerable importance, also, but the inexperienced usually attach too much, rather than too little, importance to this feature. Some authors regard emaciation and physical weakness as evidence of pellagra, but these signs are, of course, common to very many pathological conditions.

Only the typical cutaneous eruption on the backs of the hands warrants a definite and certain diagnosis of pellagra. The localization on the backs of the hands and forearms, the approximate bilateral symmetry, its sudden appearance as an erythema, gradual evolution to hyperkeratosis, with or without hyperpigmentation, the subsequent desquamation and restitution, with or without persistent atrophy, are important in the recognition of the pellagrous eruption. A dermatitis due to molds may simulate the pellagrous eruption, but such a dermatitis usually occurs elsewhere than on the backs of the hands. Roussel, however, mentions cases in which the differential diagnosis was finally decided only by the microscopic demonstration of mycelial threads in lesions on the backs of the hands. The developmental course of a mild dermatitis is usually different, also, so that continued observation may alone suffice for its differentiation.

A tentative diagnosis of pellagra is often justified without observation of the eruption. Certainly the disease is usually still present after the eruption has disappeared, and there is abundant evidence that the patient suffers from pellagra when the eruption is absent. However, such a tentative diagnosis should be abandoned if the patient does not subsequently present the eruption or confess to its earlier presence.

Prophylaxis

Preventive measures may be grouped in two classes; first, those which enhance the individual resistance to the disease, and, second, those which diminish the opportunity for the specific causative factor to attack the individual. In its endemic centers pellagra attacks only a small proportion of the population at any one time, and the physically vigorous escape it to a very large extent. The maintenance of robust physical vigor is, therefore, an excellent insurance against pellagra. In every natural community, however, there will be some tender young children, some children occasionally sick with measles or gastro-intestinal derangement, some

women in the puerperium and some old people in the decline of life. The maintenance of individual resistance therefore has its limitations.

Among measures of the second group the most effective is distance from persons suffering from the disease. Where pellagra has prevailed in the general population, there new cases may be expected to appear. Sanitary disposal of human excreta would appear to be an important means to prevent the origin of new cases of pellagra. Physical equipment, such as sewers, piped water supply and screens are very important, but sanitary instruction and particularly an adequate inspection service to insure the proper use of the equipment must not be neglected. Lunatic asylums with most modern sanitary equipment, still may have their "untidy wards."

General improvement in nutrition, especially the liberal consumption of milk and of wholesome fresh meat, plays an important part in preventing pellagra among those who have not yet contracted the disease and also in preventing recurrences in those already affected by it. Such foods probably act by enhancing the general vigor, but there may be a more specific effect, possibly by altering the intestinal bacteria or by supplying a deficiency of certain food elements or by furnishing an accessory food factor essential to nutrition.

Treatment

In treatment one has to consider the period of the active attack and the interval between attacks. Recovery from the attack occurs in about 85 per cent of the instances. In fact, more than half the attacks do not cause the patient to go to bed, and the vast majority run their course to recovery without any definite treatment. In those who do become bedridden the death rate is fairly high.

The indications are for supportive and symptomatic treatment. A comfortable bed in a clean, pleasant and moderately cool room, with a competent, interested and sympathetic nurse, almost insure recovery. The lips, mouth, teeth and pharynx should be kept scrupulously clean. Irritation of the eruption is lessened by bandaging with an ointment of zinc oxid, lanolin and vaseline. The diet should include milk as the principal element. Every effort should be made to encourage the appetite, but overfeeding to the point of distaste or nausea is dangerous. Food may be refused for two or three days without a fatal outcome. Pellagrins are very susceptible to suggestion, and the presence of recovered patients has a real therapeutic value. Conversely, a pellagrin, surrounded by friends or by nurses who regard the disease as horrible and necessarily fatal, usually dies.

Pustules, ulcers and sloughs of the skin require mild antiseptic wet dressings. The diarrhea should not be interfered with, and it is not a

contra-indication to a liberal milk diet. Peripheral neuritis and paresis require massage and precautions to avoid deformity. Mental derangement should be expected in all severe attacks. Physical restraint usually only aggravates the difficulty. Of the hypnotics probably chloral is the most effective. Morphin is not recommended. Mental cases require vigilance, for there is occasionally a real suicidal tendency. The noisy delirium of these patients renders their treatment in a general hospital rather difficult.

Complicating disorders are often of more importance than the pellagra itself. Tuberculosis, chronic alcoholism, pelvic disease in women are common complications. In institutional pellagra, undernourishment from prolonged lack of adequate food is common, and it is one of the most easily corrected complications.

After recovery from the active attack, every effort should be made to keep the general resistance of the patient at a high level. Alleviation of debilitating disorders, relief from overwork, administration of tonic drugs and especially removal to a cooler climate are to be recommended. The particularly dangerous period is the spring and early summer next following. Public charity may improve the resistance of poverty stricken pellagrins but sometimes the handicap of a particular patient cannot thus be relieved and this is usually true of well-to-do pellagrins. Such patients require regulation of their lives for several years.

The Relation of Diet to the Causes and Treatment of Pellagra . . . . . *E. V. McCollum*

Historical—Etiological Factors—Intoxication—Deficiency of Proteins—Deficiency of Vitamins—Pellagra, a Transmissible Disease—Pathology—Conclusion.

The Relation of Diet to the Cause and Treatment of Pellagra

E. V. McCOLLUM

BALTIMORE

Casal of Oviedo in Spain, who first described pellagra, associated the disease with poverty and bad nourishment. Many investigations have been directed toward the study of its cause, but the exact nature of the factors which enter into its etiology have not yet been established. The people of Oviedo ate little meat. Their diet consisted of maize, beans, peas, chestnuts, apples, pears, melons and cucumbers. All later observers agree with this early report that persons who suffer from pellagra derive their diet in great measure from vegetable foods, and that chief among these are cereal products of one kind or another.

In 1866 Roussel stated that pellagra could be cured with good food, and that without adequate dietetic measures all remedies were useless. In the light of all the extensive researches which have been conducted by many investigators, all are in agreement with Roussel's view. There is considerable difference of opinion, however, concerning the dietary factor or factors which contribute to the causation of the disease.

The early observations on the etiology of pellagra were made with no understanding of the chemical composition which is essential for the maintenance of normal physiological function, and consequently it was not to be expected that a satisfactory control of the diet or satisfactory interpretations were likely to be made. Since, however, pellagra has not been produced experimentally in animals, all our criteria as to its cause are based on studies on human subjects. As is almost always the case under such conditions, the control of the character of the diet, or observations regarding the constitution of the diet prior to the attack or recurrence, have rarely been exact and complete. In other words, the nature of the observations in all experimental studies of pellagra are not such as to constitute a rigidly controlled experiment. They do not, therefore, yield conclusive evidence or form safe basis for deductions.

It may be stated at the outset that the view that pellagra is due to an intoxication might be expected to be supported or refuted by studies of the kinds which are recorded in the literature. Strambio first propounded

the theory that pellagra is caused by the consumption of maize. This theory was revived by Lombroso, but numerous cases of the disease have been observed in persons who have never consumed any maize. Furthermore, in regions where some ate maize (corn) and others little or none, the incidence of the disease has never been found greater among the maize eaters than among those who make no use of this grain. Furthermore, the view that certain toxic substances, formed through the action of molds or other microörganisms growing in spoiled corn, are responsible for the symptoms of pellagra, find no support in investigations of the last decade.

The researches of Kossel, Fischer and Osborne on the chemistry of the proteins revealed the fact that certain proteins are lacking relatively or absolutely in certain of the amino-acids which are essential for normal nutrition. Other proteins are so constituted as to yield the indispensable amino-acids in proportions very different from the optimal for transformation into body tissues, and these are, therefore, proteins of low biological value. Since zein, the principal protein of the maize kernel, is entirely lacking in tryptophane, one of the digestion products of proteins, it was suggested by Sandwith that pellagra might be explained by the lack of this amino-acid. Other investigators, especially Voegtlin, and Goldberger have reported results of studies with certain diets in pellagrous districts and with others which proved effective for the cure of the disease, which are in harmony with the view that pellagra is induced by a lack of certain amino-acids in the diet. It is not yet proven that this is the true explanation of the cause of the disease, however, and indeed Voegtlin has recently published experimental data which, if substantiated, will serve as conclusive proof that pellagra is due to deficiency of a substance or substances which should be classed with the vitamins.

Voegtlin has recently reported experiments on pellagrins in which the alcoholic extracts of fat-free liver or thymus were administered to patients who were maintained upon a diet which had been shown not to cause any improvement in patients suffering from the disease, or even to prevent them from gradually getting worse. The administration of the extractive material from these glands is reported to have given results comparable in every way to those seen when patients suffering from "uncomplicated pellagra" are given a diet containing liberal amounts of milk, eggs, meats and fresh vegetables.

There are some remarkable features about this report which are well worthy of further observations. In the first place, alcohol is not an effective solvent for amino-acids nor inorganic salts, so that the preparations given the patients could not be regarded as of a nature suitable for the enhancement of the protein moiety or the inorganic moiety of the diet, both of which in the typical "pellagrous" diet are deficient and of poor quality. In the second place, it seems remarkable that improvement so pronounced

as that reported could have resulted from the administration of a hypothetical "anti-pellagra vitamin" which the extracts may have furnished, when the diet was otherwise so poorly constituted. If the studies reported by Voegtlin should be confirmed, they will, however, effectively establish pellagra as a deficiency disease in the same sense as are the other syndromes which are included under that term.

The view that pellagra is due to specific starvation for a vitamin or vitamins was first suggested by Funk, who, however, was not able to offer any evidence in support of his contention. It has been shown by McCollum and Simmonds that diets of the type commonly employed in pellagrous districts can be supplemented by the addition of certain mineral salts, purified protein and one of the vitamins (fat-soluble A) so as to render them complete for the nutrition of the rat. If one were justified in accepting data of this kind obtained in animal studies, as applying directly to the elucidation of the human problem, this would constitute definite proof that pellagra is not a disease due to lack of a vitamin. We have one proven case, however, of the immunity of one species of animal to a typical deficiency disease due to its ability to synthesize the vitamin which, when lacking in the diet, leads to the development of the specific syndrome. The rat does not develop scurvy when confined to a diet which produces this disease in the guinea pig within two to four weeks. Young rats may grow to maturity on such a diet and show no appearance of abnormality. Miss Parsons, working in the author's laboratory, showed that the livers of such rats would induce a prompt cure of guinea pigs which were suffering from acute scurvy. The rats had not obtained the antiscorbutic substance from their food, and must, therefore, have been able to synthesize it from some other complex in their diet. It is possible that a similar situation may exist in the case of the rat restricted to a diet which would permit or cause the development of the symptoms of pellagra in man. Such an experiment as the satisfactory nutrition of young rats on a diet on which man has developed the disease, when the diet has been enhanced by the addition of purified food substances, does not eliminate the possibility that the pellagrous diet, supplemented so as to be complete for the rat, would still be incomplete for man.

The cause of pellagra has recently been attributed by Wilson to inadequacy of the diet as respects quantity and quality of protein. His experiments were in essential features comparable to earlier ones by Goldberger. We may profitably consider certain of these very briefly.

Goldberger, Waring and Willets observed that the diet in two orphanages in Mississippi were derived in great measure from bolted white flour, degerminated cornmeal, molasses, fat pork, and a few vegetables. The number of pellagrins in one of these institutions, M. J., between January and September, 1914, was 70, and in the other, B. J., 130. They replaced a part of the calories of these diets by oatmeal in place of corn grits, and

adding meat, milk, eggs and legume seeds. The result of this modification of the diet was that during 1915 there were no new cases or recurrences of the disease. In similar orphanages in which there were no comparable changes in the diet there were recurrences to the extent of 58 to 75 per cent. Goldberger and his associates likewise eradicated pellagra from the State Insane Asylum of Georgia through similar dietetic treatment. Judging from what we now know about the dietary properties of many of our more important natural foodstuffs, one may safely assert that the important modifications in the diets just described, which led to improvement of the condition of the inmates of institutions with respect to pellagra, were due to the addition of milk, meats and eggs, especially milk.

Wilson reported similar results in his work with the inmates of the Asassia Asylum for the Insane at Cairo. The diet contained 100 grams of meat, 50 grams of milk, and 300 grams of fresh vegetables, the character of which was not named. Otherwise it consisted essentially of cereal products. Through the addition of 45 grams of meat and 50 grams of milk to the diet of each inmate, the death rate from pellagra during the following year was diminished by nearly 50 per cent. Wilson regarded the modification of the institutional diet as of such a nature as not to modify in an important way any factors other than the quality and amount of protein. He drew the deduction that the protein factor is the most significant one in the causation of pellagra.

There is a criticism which one is justified in directing against all these investigations. The improvement in the condition of pellagrins, or the reduction of the rate of incidence of the disease in any group of persons who are taking the milled cereal type of diet, on the addition of such complex natural foods as milk, eggs or meat, cannot with safety be interpreted as meaning that improvement of the diet with respect to protein has induced the benefit. It is entirely defensible in the light of the experimental observations now available on animals to view these experiments in an entirely different light.

We must emphasize that all our progress in the study of nutrition in recent years has pointed to the importance of recognizing borderline malnutrition as a condition difficult of detection, yet fraught with menace to the individual. The animal body is remarkably sensitive to the quantitative relations between certain of the mineral elements contained in the diet, notably calcium and phosphorus, and also to lack of one or another of the vitamins as well as to the quality and amount of protein which the food supply contains. Two or more of these factors may operate simultaneously to disturb the metabolic equilibrium, and even such modifications of the diet as the addition of 45 grams of meat and 50 grams of milk to a diet of the type described by Wilson, may easily be regarded as sufficient to make a pronounced difference in the well-being of a patient, not alone because of improvement of the protein moiety of the diet, but of the

inorganic factors and vitamins as well. The sum of the enhancement of all these factors rather than of any single one of them should be given credit for the results observed.

A further point should be emphasized in connection with the experiments of Wilson. His basis for the estimation of the biological value of the proteins which entered into the diets of his patients were the data furnished by Thomas, and which have been frequently employed in recent years for strengthening conclusions which were drawn from faulty experimental data. Thomas's figures represent nothing more than digestion coefficients of doubtful accuracy, and cannot be looked upon as representing the biological values of the proteins in the sense that this term is now used. Thomas designated his figures as representing the "utilization" of the different proteins which he studied. No one would to-day think of conducting experiments in the manner in which his were carried out.

It has been held by some investigators, especially by the Thompson Pellagra Commission of the New York Post-Graduate School of Medicine, that pellagra is a transmissible disease. They based their conclusion on the remarkable incidence of the disease at the end of winter. They were inclined to incriminate the fly as a carrier of the infection. This view has not been generally accepted, and has little direct evidence in support of it. The occurrence of new cases principally in the spring is equally well accounted for by Goldberger on the basis of adherence of the subjects to a faulty diet during three to four winter months. This period is, he believes, necessary for the effects of the faulty nutrition to become manifest.

Goldberger attempted to settle the question of the etiology of pellagra by an attempt to induce pellagra in man by the continued employment of a faulty diet. He restricted eleven volunteers among the prisoners at the Mississippi State Prison during six months to a diet composed essentially of the following list of foods: Bolted wheat flour, degerminated cornmeal, polished rice, starch, sugar, molasses, sweet potatoes, fat pork, cabbage, collards, turnip greens and coffee. I calculated from the data furnished by Goldberger, that less than four per cent of the total calories of the diet were derived from the sweet potatoes, cabbage, collards and turnip greens altogether. The diet was, therefore, essentially derived from milled cereal products, molasses and fat pork. Six of the eleven men were diagnosed as having at the termination of the experiment incipient symptoms of pellagra. McNeal and others have insisted that the diagnosis was made on inadequate evidence. The question as to whether faulty diet of the type described can induce pellagra still remains to be fully established.

There are excellent reasons for believing that the most important lesion in pellagra is a degeneration of certain centers in the cord. This has been especially emphasized by Vedder. The remarkable bilateral

symmetry of the skin lesions can best be accounted for on the assumption that they have their origin in damage to certain centers in the cord.

Vedder further points to the similarity of the symptomatology of pellagra and of scurvy on the one hand, in that diarrhea, enteritis, ulceration of the intestine and hemorrhage into the mucous membranes are observed in both conditions. He also emphasizes that there are similar nervous symptoms in pellagra and scurvy.

On the other hand Vedder calls attention to the similarities in the lesions in the nervous system and in the symptomatology referable to the nervous system in pellagra and beri-beri. After discussing this point he concludes: "Now if we compare this picture with the changes found in the cord in beri-beri, we find that pellagra is characterized by the same scattered degeneration of the fibers and similar changes in the cells of the cord."

Modern studies in nutrition have made it clear that it will rarely if ever happen in everyday life, that the diet of man will be of such a nature as to induce one of the deficiency diseases without complications arising from dietary deficiencies of kinds not related to the specific symptoms which predominate and decide the nature of the diagnosis. It has certainly been true that no case of beri-beri has ever developed which was not also at least a borderline case of scurvy as well. Without doubt deficiency diseases tend to occur together, either as well marked conditions or as superimposed borderline complexes forming syndromes which vary to some extent in individuals and lead to confusion.

In conclusion it may be said that pellagra can at present be viewed either as an infection transmitted by some agency such as an insect, or as due to specific starvation for some one or more dietary essential. The first view is supported especially by the epidemiological studies of the Thompson Pellagra Commission, and Jobling and Peterson; the latter by almost all other investigators, notably Goldberger, Wilson, Voegtlin and others. It is not possible to decide with certainty from the experimental data at present available which theory is correct, but the evidence seems preponderating that faulty diet is the underlying causative agent, either inducing the disease in a manner analogous to the recognized deficiency diseases, beri-beri, scurvy, and ophthalmia of dietary origin, or in a more complicated way as rickets is now known to be caused by poorly constituted diets, or by preparing the body for the reception of some infective agent owing to the breaking down of the natural barriers of resistance. The remedy in either case is entirely clear. It consists in the establishment of a more satisfactory dietary regimen in those regions where the disease prevails.

INDEX

Absorption, theory of control of, by internal secretion of pancreas, 675.
— in typhoid fever, 116.
Acetone bodies, in blood and urine, determination of, 84.
Acetonuria, carcinomatous, metabolism in, 632.
Achlorhydria, metabolism in, 612.
Achondroplasia, See Infantilism.
Achondroplasiac dwarf, metabolism of, table, 827.
Achylia, metabolism in, 612.
Achylia pancreatica, metabolism in, 674.
Acid action in osteomalacia, 752.
Acid-base balance of the body, abnormal variation in, compensated alkali excess, 72.
— — compensated CO_2 excess, 72.
— — uncompensated alkali excess, 68.
— — uncompensated CO_2 deficit, 70.
— methods for determining state of, 76.
— — of acetone bodies in blood and urine, 84.
— — alkali retention test for alkali deficit, 81.
— — of the alveolar CO_2 tension, 82.
— — calorimetric dialysis method for pH, 81.
— — collection and treatment of blood samples, 78.
— — electrometric determination of the plasma pH, 80.
— — estimation of blood bicarbonate and pH, 77.
— — of excretion rate of ammonia and free acid, 83.
— — gastrometric determination of whole blood or plasma bicarbonate, 79.
— — titrimetric determination of plasma or serum bicarbonate, 80.
— normal, alkali reserve, 64.
— — ammonia formation, 56, 66.
— — buffers of the blood, alkali reserve, 64.
— — — interchange of buffer effects, between blood cells and plasma, 61.
— — — — between the blood and the tissues, 62.
Acid-base balance of the body, normal, buffers of the blood, laws of, 57.
— — — maximum efficiency of action of, 59.
— — — nature of, 57.
— — — neutralization of acid by, 57.
— — — physiologically available alkali of the bicarbonate and of other blood buffers, 63.
— — excretion of acid by the kidneys, 56, 65.
— — mechanism for maintenance of, buffers of the blood, 56.
— — — kidneys, to excrete acid products, 56, 65.
— — — lungs, to accelerate the rate of CO_2 excretion, 56, 64.
— — — organism forming ammonia, 56, 66.
— — normal bicarbonate concentration of blood plasma and other body fluids, 54, 63.
— — normal hydrogen ion concentration of blood plasma and other extracellular fluids, 54, 57.
— — respiratory regulation of free H_2CO_3 of the blood, 64.
— normal and abnormal variation in, representation of combined variations in blood bicarbonate and hydrion concentration, 67.
— — and resultant effects on physiological functions, 67.
— normal variations in, 72.
— — compensated alkali deficit, 73.
— — compensated CO_2 deficit, 73.
— — uncompensated alkali deficit, 75.
— — uncompensated CO_2 excess, 74.
— relation of changes in, to the changes in other body fluids, 76.
Acid sodium urate, 465, 466.
— solubility of, and temperature, 466.
Acidosis, after anesthesia, 92.
— and diabetes, 277.
— in cyclic vomiting of children, cause of, 92.
— — diagnosis of, 92.
— — therapy for, 92.
— — type of, 92.
— definition of, 52.

Acidosis, diabetic, clinical conditions in, comparison of, with results of different tests for alkali deficit, table, 85.
——— diagnosis of, 88.
——— therapy for, 89.
——— type and cause of, 88.
— diagnosis of, in cyclic vomiting of children, 92.
——— in diabetes, 88.
——— in diarrhea of infants, 91.
——— general considerations concerning, 86.
——— in nephritis, 90.
— in diarrhea of infants, diagnosis of, 91.
——— therapy for, 92.
——— type and cause of, 90.
— due to oxygen lack, 544.
— historical data on, 51.
— nature of, 52.
— in nephritis, 313.
——— diagnosis of, 90.
——— therapy for, 90.
——— type and cause of, 89.
— in pneumonia, lobar, 130.
— rôle of, in uremia, 391.
— in shock, 256.
— therapy of, bicarbonate, administration of, 86.
——— in cyclic vomiting of children, 92.
——— in diabetes, 89.
——— in diarrhea of infants, 92.
——— general consideration concerning, 86.
——— in nephritis, 90.
Acne vulgaris, associated, with diet, 698.
——— with digestive disturbances, 696.
——— with miscellaneous causes, 704.
Acroasphyxia, associated with miscellaneous causes, 704.
Acromegaly, and osteoporosis, 761.
Acute yellow atrophy of liver, composition of liver in, 654.
— liver functional tests in, 653.
Addison's disease, diarrhea of, metabolism in, 640.
Adenin, formula for, 413.
Adiposis dolorosa, 40.
— etiology of, 41.
— pathology of, 41.
— prognosis of, 41.
— symptoms of, 40.
Adrenal gland, and obesity, 39.
Adrenal glands, relation between disturbances of bone metabolism and, 765.
Age, as factor, in cystinuria, 524.
——— in diabetes insipidus, 863.
——— in obesity, 34.
——— in pellagra, 902.
Albuminuria, and eclampsia, 835.
Alimentary pentosuria, 292.
Alimentary tract, in obesity, 35.
Alkali excess, in acid-base balance of the blood, compensated, 72.
——— uncompensated, 68.
Alkali retention test for alkali deficit, 81.
Alkaline condition of intestines, in metabolic disturbances of infancy, 784.
Alkalinuria, 461.
Alkalosis, in progressive muscular dystrophy, 724.
——— with creatinuria, 724.
——— with hypoglycemia, 724.
Alkapton, formation of, in body, 506.
——— table of alkapton formers, 507.
Alkaptonuria, character of, 501.
— and consanguinity, 502.
— definition of, 501.
——— intestinal bacterial origin, objections to, 508.
——— properties of alkapton formers in body, 508.
——— table of alkapton formers, 507.
——— transformation of tyrosin to homogentisic acid, 507.
— history of, 503.
— hypothesis of, as due to closure of one of two paths normally followed by aromatic amino acids, 511.
——— as due to failure to break down homogentisic molecule, 510.
— metabolic findings in, 513.
— occurrence of, 501, 503.
— oxidation in and benzol ring, 511, 513.
— prognosis in, 514.
— relationship between ochronosis and, 514.
— substances influencing excretion of, 509.
— symptoms of, 501.
— table showing daily H : N ratios, 512.
— treatment of, 514.
— urine of, black, 501.
——— glycosuric acid in, 503.
——— homogentisic acid in, 503.
——— amount excreted, 511.
——— formation of, 508.
——— formation of, a pathological process, 510.

Alkaptonuria, urine of, homogentisic acid in, formula for, 504.
— — — synthesis of, Baumann and Frankel, 504.
— — — — — Neubauer and Falta, 506.
— — — — — Osborne, 505.
— — — transformation of tyrosin to, 507.
— — isolation of substances in, 503.
— — protocatechinic acid in, 503.
— — pyrocatechol in, 503.
— — substances in, 503.
— — uroleucic acid in, 503.
Allantoin, formula for, 414.
— relation of, to uric acid, 414.
Allen method of starvation in diabetes, 26.
Alloxuric bases, 413.
Alveolar CO_2 tension, determination of, 82.
Ambard's coefficient of urea excretion, 358.
Amino acid nitrogen, in urine, amounts found by various investigators, table, 475.
Amino acids, leucin, in urine, 476.
— in nephritis, 331.
— tyrosin, in urine, 476.
— in urine, increased amount of, in pathological conditions, or aminoaciduria, 475.
Aminoaciduria, conditions causing, 476.
Ammonia formation, 56, 66.
Ammonia and free acid, determination of excretion of, 83.
Amyotonia congenita, metabolism in, 730.
Anabolism, bone, 735.
Anaphylaxis, active, 197.
— anti-, 198.
— degrees of hypersensitiveness, non-specific alteration of, 216.
— etiology of, 205.
— — cellular and humoral theories, 205.
— — evidence regarding theories of, 206, 207.
— — intracellular theory, 206, 211.
— experimental, differentiated from natural idiosyncrasies, 227.
— — pathological physiology of, 198.
— — — blood and blood-forming organs, 203.
— — — blood pressure, 201.
— — — capillaries, 201.
— — — cardiovascular mechanism, 201.
Anaphylaxis, experimental, pathological physiology of, in cat, 199.
— — — in dog, 199, 202.
— — — gastro-intestinal tract, 202.
— — — in guinea-pig, 199.
— — — heart, 202.
— — — liver, 203.
— — — lungs, 201.
— — — in man, 200.
— — — muscles, 204.
— — — in rabbit, 199.
— — relationship of, to diseases in man, 218.
— heat regulation in, 213.
— historical, 197.
— hypersensitiveness, degrees of, 224.
— — — variations in, 225.
— — forms of, 222.
— — materials producing, variety of, 226.
— idiosyncrasies of, 222.
— — natural, differentiated from experimental anaphylaxis, 227.
— introduction to, 197.
— metabolism in, asthma, 229.
— — heat regulation, 213.
— — protein, 209.
— — respiratory, 212.
— — urticaria, 229.
— multiple sensitizations, 227.
— non-specific alteration of the degrees of hypersensitiveness, 216.
— passive, 197.
— pathological physiology of, in experimental anaphylaxis, 198.
— — — blood and blood-forming organs, 203.
— — — blood pressure, 201.
— — — capillaries, 201.
— — — cardiovascular mechanism, 201.
— — — in cat, 199.
— — — in dog, 199, 202.
— — — gastro-intestinal tract, 202.
— — — in guinea pig, 199.
— — — heart, 202.
— — — liver, 203.
— — — lungs, 201.
— — — in man, 200.
— — — muscles, 204.
— — — in rabbit, 199.
— — serum and cellular ferments, 214.
— pathology of, 208.
— phenomena of, 197.
— place of formation of poisonous substance which brings about anaphylactic shock, 205.
— protein intoxication, 230.

Anaphylaxis, protein metabolism in, 209.
— quantitative relations between sensitizing dose, length of incubation period, minimal anaphylactic dose and minimal desensitizing dose, 198.
— reactions of, from drugs and from protein substances, attempts to correlate, 226.
— — manner of producing, 224.
— refractory and sensitive conditions, 198.
— relationship of experimental anaphylaxis to diseases in man, 218.
— respiratory metabolism in, 212.
— sensitization, relative susceptibility of different species to, 228.
— — spontaneous, diseases associated with, 228.
— sensitizations, multiple, 227.
— serum and cellular ferments in, 214.
— serum disease, blood coagulation in, 221.
— — clinical picture of, 218.
— — definition of, 219.
— — factors concerning development and recovery from 221.
— — incubation period of, 219.
— — mechanism causing, 221.
— — reactions in, accelerated, 220.
— — — immediate, 220.
— — — normal, 219.
— — — types of, 219.
— — tissue changes in, 220.
— theories of, cellular, 205.
— — evidence regarding, 206, 207.
— — humoral, 205.
— — intracellular, 206, 211.
Anchylostomiasis, metabolism in, 636.
Anemia, Banti's disease, purin metabolism in, 580.
— bothriocephalus, purin metabolism, in, 581.
— congenital hemolytic jaundice, purin metabolism in, 581.
— hemolytic, iron metabolism in, 588.
— — nitrogen partition in, 584.
— — protein metabolism in, 576.
— — purin metabolism in, 580.
— metabolism in, basal, 567.
— — — compensatory factors in anemic states, 570.
— — — experimental and clinical observations, 567.
— — high, causes of, 573.
— — influence on, of diet, 594.
— — — of röntgen-rays and radium, 601.
Anemia, metabolism in, influence on, of splenectomy, 596.
— — — of transfusion, 594.
— — iron, 585.
— — — table of, 587.
— — mineral, phosphoric acid, calcium and magnesium, 590.
— — — sulphur, 591.
— — protein, hemolytic varieties, 576.
— — — nitrogen balance, 574.
— — purin, 579.
— — — experimental and clinical observations, 580.
— — — partition of other nitrogenous constituents of urine, 583.
— nitrogen balance in, 574.
— pernicious, metabolism in, basal, 568.
— — nitrogen partition in, 584.
— secondary, metabolism in, purin, 580.
— — — respiratory, 568.
— — — table, 569.
— treatment of, by diet, influence of, on metabolism, 594.
— — by röntgen-rays and radium, influence of, on metabolism, 601.
— — influence of, on metabolism, 596.
— — — influence of, on metabolism, 594.
Anemic states, compensatory factors in, 570.
Anesthesia, acidosis after, 92.
Angioneurotic edema, associated with diet, 698.
— with digestive disturbances, 697.
— due to protein poisoning, 158.
Anti-anaphylaxis, 198.
Appendicitis, metabolism in, 631.
Arterial blood, observations on, 546.
Arterial pressure, increased, in nephritis, 397.
— — acute, 398.
— — cause of, 401.
— — cause of, blood volume and plethora, 402.
— — — epinephrin, 404.
— — — increased vasomotor tone, 403.
— — — insufficient renal function, 401.
— — — internal secretions derived from kidney, 405.
— — — viscosity of blood, 402.
— — chronic diffuse (parenchymatous), 399.
— — essential hypertension and primary contracted kidney, 400.

Arterial pressure, increased, influence on, of food products, 406.
— — nephrosis, 398.
— — occurrence of, 398.
— — and secondary contracted kidney, 399.
Arteriosclerosis, and osteitis deformans, 765.
— osteomalacia and, 761.
Arthritis, primary atrophic, metabolism in, 773.
— — metabolism in, table of observations, 775, 776, 777.
— primary hypertrophic, metabolism in, 773.
— — metabolism in, table of observations, 774.
Arthropathies, classification of, 772.
— — gout, 772.
— — primary atrophic arthritis, 773.
— — secondary to infections, 773.
— — trophic arthropathies secondary to disease of central nervous system, 772.
Athreptic infants, metabolism in, 799.
Ascites, in cirrhosis of liver, 158.
— of edema, 157.
Asthma, anaphylaxis in, 229.
Atony of the stomach, metabolism in, 622.
Atophan therapy, in gout, 448.
Atrophy of liver, acute yellow, composition of liver in, 654.
— — live functional tests in, 653.
Auto-intoxication, as cause of intestinal obstruction, 633.
— factors in, 634.

Bacteria, intestinal, rôle of, in infantile diarrhea, 790, 791.
— rôle of, in decomposition of cystin, 521.
Banti's disease, purin metabolism in, 580.
Basal metabolism, formulæ for predicting in healthy adults, 32.
Basal metabolism, in anemia, 567.
— in children, 32.
— in fever, and Van't Hoff's law, 121.
— in leukemia, 567.
— meaning of term, 31.
— in pneumonia, lobar, 124.
— in shock, 257.
Baths, in treatment of edema, 194.
Bence-Jones protein, in blood and lymph, 487.
— in bone, question of, 485.
— chemical nature of, 486.
Bence-Jones protein, discovery of, 485.
— digestive products of, 486.
— history of, 485.
— introduction to, 485.
— metabolic studies of cases excreting, tables of Folin and Denis, 490, 491.
— — tables of Hopkins and Savory (multiple myeloma case), 492, 493.
— — tables of Hopkins and Savory (three different cases), 494, 495.
— — tables of Seegelken (multiple myeloma), 495, 496.
— — tables of Walters (multiple myeloma), 496, 497, 498.
— and multiple myeloma, metabolic studies of, tables, Hopkins and Savory, 492, 493.
— — — — — Seegelken, 495, 496.
— — — — — Walters, 496, 497, 498.
— — myelopathic proteosuria (Kahler's disease), 498.
— origin and nature of, theories regarding, origin from bone, 489.
— — possible derivation from blood proteins, 488.
— — product of abnormal metabolism, 490.
— — proteose relationships, 488.
— and proteosuria, 487.
— treatment of, 500.
— in urine, 486.
Benzol, influence of, on metabolism, in blood diseases, 604.
Beriberi, in breast-fed children, 249.
— causes of, 250.
— definition of, 889.
— diagnosis of, 893.
— etiologic relationship between pellagra and, theory of, 900.
— etiology of, 889.
— occurrence of, 889.
— pathology of, 890.
— symptomatology of, 892.
— treatment of, prophylactic, 894.
— — symptomatic, 894.
— — specific, with vitamin preparations, 894.
— — — with yeast preparations, 897.
— types of, 892.
Bicarbonate, administration of, in acidosis, 86.
Bicarbonate concentration, normal, of blood plasma and other body fluids, 54.
Bile, composition of, 647.
— — bile pigments, 648.
— — bile salts, 648.
— — cholesterol, 649.

Bile, composition of, fat, 649.
——— mineral substances, 649.
— excretion, daily, 647.
——— stimulation of, 647.
— storing and ejection of, 647.
Bile-pigment metabolism, regulatory function of liver in, 558.
Bile pigments, chemistry of, 648.
Bile salts, chemistry of, 648.
Bilirubin, 648.
Blood, acetone bodies in, determination of, 84.
— analysis of, in erysipelas, 139.
— arterial, observations on, 546.
— Bence-Jones protein in, 487.
— buffers of, see Buffers of the Blood.
— calcium of, in nephritis, 348.
— chemical changes in, in shock, 258.
— chlorids of, in nephritis, 346.
— cholesterol content of, in nephritis, 342.
— composition of, in edema of heart failure, carbon dioxid content, 172.
——— oxygen content, 172.
——— number and volume of red cells, 173.
——— reaction of blood, 173.
——— sodium chlorid content of plasma, 173.
——— summary, 174.
— condition of, in infantile diarrhea, 793.
— constituents of, in pneumonia, lobar, 129.
——— in tuberculosis, 138.
— creatinin in, in nephritis, comparative value of uric acid, urea and, 330.
— destruction and regeneration of, destruction of red blood-cells, 554.
——— fragmentation, 555.
——— hemolytic process, 555.
——— mechanism of, 554.
——— nature of stimulus to regeneration, 555.
——— newer aspects of, 553.
——— phagocytosis, 554.
——— regeneration of red blood-cells, 555.
——— regulatory influence of spleen in, 562.
——— tests of bone-marrow activity, 556.
— in edema, volume of, 170.
— examination of, in scurvy, 885.
— fructose in, 298.
— nitrogen in, in pregnancy, 851.
Blood, nitrogenous metabolites and fats of, chemical changes in, 592.
— non-protein nitrogen of, in nephritis, 319.
——— relation of, to urea, 323.
— non-volatile products of metabolism in, 549.
— pancreatic ferments in, testing for presence of, 664.
— phosphates of, in nephritis, 348.
— plasma bicarbonate, estimation of, 77.
——— gasometric determination of, 79.
——— titrimetric determination of, 80.
— in pregnancy, changes of urea nitrogen in, 854.
——— cholesterol content of, 858.
——— creatinin nitrogen in, 855.
——— examination of, by modern methods, 848.
— urea of, in nephritis, 321.
——— comparative value of uric acid, creatinin and, 330.
——— relation of, to total non-protein nitrogen, 323.
— uric acid in, in gout, 428.
——— in health, 425.
——— in nephritis, comparative value of urea, creatinin and, 330.
— uric acid nitrogen in, in pregnancy, increase of, 857.
— viscosity of, and arterial hypertension in nephritis, 402.
Blood bicarbonate, estimation of, 77.
Blood and blood-forming organs, effect on, of anaphylaxis, 203.
— metabolism of, pathological, blood destruction and regeneration, mechanism of, 554.
——— newer aspects of, 553.
——— regulatory influence of spleen in, 562.
——— hemoglobin pigment metabolism, breaking down of hemoglobin, 558.
——— building up of hemoglobin, 558.
——— methods of determining rate of hemoglobin destruction, 561.
——— regulatory influence of spleen in blood formation and destruction, 562.
——— introduction to, 553.
Blood cells, red, destruction of, 554.
——— regeneration of, 555.
Blood diseases, metabolism in, anemia, basal metabolism, 567.
——— bothriocephalus, purin metabolism, 581.

Blood diseases, metabolism in, anemia, hemolytic, iron metabolism, 588.
— — — — purin metabolism, 580.
— — — nitrogen balance, 574.
— — — protein metabolism, 574.
— — — purin metabolism, 579.
— — — secondary, basal metabolism, 568.
— — — — table, 569.
— — — — purin metabolism, 580.
— — chemical changes in nitrogenous metabolites and fats of blood, 592.
— — chlorosis, basal metabolism, 568.
— — — — table, 569.
— — — iron metabolism, 588.
— — — purin metabolism, 580.
— — hemorrhage, mineral metabolism, 586.
— — influence on, of some measures of treatment, benzol, 604.
— — — diet, 594.
— — — röntgen rays and radium, 601.
— — — splenectomy, 596.
— — — transfusion, 594.
— — jaundice, congenital hemolytic, purin metabolism, 581.
— — leukemia, basal metabolism, 567.
— — — — table, 571.
— — — iron metabolism, 589.
— — — protein, 578.
— — — purin metabolism, 579.
— — mineral, 585.
— — — iron, 585.
— — — phosphoric acid, calcium and magnesium, 589.
— — — sulphur, 591.
— — pernicious anemia, basal metabolism, 568.
Blood chemistry findings in influenzal pneumonia, 131.
Blood flow, in edema, rate and volume of, 170.
Blood gases, observations on, 546.
Blood lipoids in nephritis, 341.
Blood plasma, chlorid content of, in acute nephritis, table, 176.
— normal bicarbonate concentration of, 54.
— normal hydrogen ion-concentration of, 54.
Blood pressure, effect on, of anaphylaxis, 201.
— influence on, of food products, 406.
— in nephritis, 313.
Blood proteins, possible derivation from, of Bence-Jones protein, 488.
Blood samples, collection and treatment of, in determining acid base balance of body, 78.
Blood serum analysis, in sodium bicarbonate edema, 167.
— in war-edema, 168.
Blood sugar, in nephritis, 343.
— See also Glucose.
Blood volume, and increased arterial pressure in nephritis, 402.
Bone, Bence-Jones protein in, question of, 485.
— origin from, of Bence-Jones protein, 489.
Bone anabolism, 735.
Bone catabolism, 735, 736.
Bone-marrow activity, tests of, 556.
Bones, composition of, change in, in rickets, 743.
— — in disease, 737.
— — — osteomalacia, 738.
— — effect on, of calcium, magnesium and strontium content of the diet, 742.
— — magnesium, disproportionate increase of, in artificial osteomalacia, 741.
— — normal, 738.
— — (normal and in osteomalacia), calcium oxid percentage, in bone ash, 739.
— — — — in dried bone, 738.
— — — magnesium oxid, in bone ash, 740.
— — — — in dried bone, 740.
— — — magnesium percentage, 739.
— — — magnesium phosphate in bone ash, 740.
— — — phosphate percentage, in bone ash, 739.
— — — — in dried bone, 39.
— — ratio of Ca : Mg (normal and in osteomalacia), in bone ash, 741.
— — — in dried bone, 741.
— — sulphur percentage, normal and in osteomalacia, 743.
— decalcification of, in arteriosclerosis, 761.
— — in obstructive jaundice, 761.
— malnutrition of, 764.
— metabolism of, 734.
— — abnormal, cause of, 752.
— — calcium, normal and in osteomalacia, 738, 739.
— — in different stages of osteomalacia, 770, 771.
— — in disease, 733.
— — — composition, 737.

Bones, metabolism of, in disease, experiments in osteomalacia, 744.
— — — calcium, 744.
— — — calcium balance, comparison of, in three stages of disease, 748.
— — — experiments in rickets, 748.
— — — intake and outgo of calcium oxid and magnesium oxid, 746, 747.
— — — magnesium metabolism, 745.
— — — sulphur metabolism, 745.
— — — ten day observation, 745.
— — effect on composition of, of calcium, magnesium and strontium content of the diet, 742.
— — etiology of disturbances of, acromegaly, 761.
— — — adrenals, 766.
— — — arteriosclerosis, 761.
— — — calcareous metastases, 761.
— — — calcification of muscles and organs, 761.
— — — diet deficient in calcium, 764.
— — — divergence of nature of, 766.
— — — food shortage, 769.
— — — hypophysis, 767.
— — — obstructive jaundice, 761.
— — — osteomata and calcification of various tissues, 763.
— — — other than pregnancy and lactation, 761.
— — — oxalic acid or oxalates in food, 768.
— — — parathyroid glands, 767.
— — — renal stones, 761, 762.
— — — thymus, 767.
— — — thyroid gland, 766.
— — — transmittable infectious agent in osteomalacia and rickets, 766.
— — — vitamines, 769.
— — histological examination in osteitis deformans, 751.
— — — in osteomalacia, 750.
— — — in rickets, 749.
— — magnesium, 739, 740.
— — normal, 735.
— — in osteomalacia, acid action in, 752.
— — — puerperal, need of calcium as a cause of, 756.
— — — relation of ovaries, 754.
— — overproduction and, 769.
— — phosphate, normal and in osteomalacia, 739.
— — ratio of Ca : Mg (normal and osteomalacia), in bone ash, 741.
— — — in dried bone, 741.
Bones, metabolism of, sulphur percentage in dried bone, 743.
— — summary of observations, 751.
Bothriocephalus anemia, purin metabolism in, 581.
Buffers of the blood, 56.
— alkali reserve, 64.
— interchange of buffer effects, between the blood and the tissues, 62.
— — between blood cells and plasma, 61.
— laws of, 57.
— maximum efficiency of buffer action, 59.
— nature of, 57.
— neutralization of acid by, 57.
— physiologically available alkali of the bicarbonate and of other blood buffers, 63.

Cachexia, edema in, 158.
Caffein, formula for, 414.
Calcareous metastases, 761.
Calcium, of the blood in nephritis, 348.
— need of, as a cause of puerperal osteomalacia, 756.
Calcium balance, in osteomalacia, comparison of, in three stages of disease, 748.
— in pregnancy, 757.
Calcium deficiency in diet, disturbances of bone metabolism due to, 764.
Calcium metabolism, 459.
— in blood diseases, 589.
— in osteomalacia, 744.
— relationship between bone metabolism, the thymus, and, 767.
Calcium oxid, percentage of, in bone ash, 739.
— — in dried bone, 738.
Calculi, cystin, 468.
— — dietetic and medicinal treatment of, 472.
— oxalate, 462.
— — dietetic and medicinal treatment of, 470.
— phosphate, 458.
— — dietetic and medicinal treatment of, 468.
— uric acid, 465.
— — dietetic and medicinal treatment of, 468.
— xanthin, 467.
— — dietetic and medicinal treatment of, 472.
Caloric diets, "optimal," in diabetes, 285.

Calorimetry, in malarial fever, direct and indirect, 144.
— in typhoid fever, direct and indirect, 100.
Cammidge reaction in the urine, 305.
Capillaries, effect on, of anaphylaxis, 201.
Capillary permeability and edema, 169.
Carbohydrate metabolism, disturbances of, other than in diabetes, glycuronic acid, 305.
— — — heptosuria, 304.
— — — maltosuria, 303.
— — — fructosuria, 296.
— — — galactosuria, 301.
— — — introduction to, 289.
— — — lactosuria, 301.
— — — pentosuria, 292.
— effect on, of oxygen-lack, 543.
— in nephritis, blood sugar, 343.
— — utilization of carbohydrates, 343.
— in typhoid fever, 109.
— in undernutrition, 10.
Carbohydrates, chemical nature of, note on, 290.
— deficiency of, in metabolic disturbances of infancy and childhood, 804.
— in food supply of diabetes, 283.
— and the liver, 643.
— as source of glucose supply, 270.
Carbon dioxid content of blood in heart failure, 172.
Carcinoma of intestines, metabolism in, 619, 638.
Carcinomatous acetonuria, metabolism in, 632.
Cardiopathies, gastric disturbances in, and metabolism, 623.
Cardiovascular disease, dermatoses associated with, 699.
Cardiovascular mechanism, effect on, of anaphylaxis, 201.
Castration, in puerperal osteomalacia, 755, 759.
Catabolism, bone, 735, 736.
Cell metabolism, and edema, 166.
Cell respiration, and edema, 166.
Chlorid content, of blood, in acute nephritis, 176.
— of edema fluids, 162.
— — table, 163.
Chlorid metabolism, in pneumonia, lobar, 127.
Chlorid threshold in nephritis, 363.
— — Atchley's observations, 365.
— — formulæ of Ambard and Weil, 364.
Chlorid threshold in nephritis, McLean's observations, 365.
— — other investigators on, 366.
Chlorids of the blood, in nephritis, 346.
— influence of, in edema, 187.
— in malaria, 144.
Chlorin balance in fasting man, table, 15.
Chlorosis, metabolism in, iron, 588.
— — mineral, phosphoric acid, calcium and magnesium, 590.
— — — sulphur, 591.
— — purin, 580.
— — respiratory, 568.
— — — table of, 569.
— nitrogen partition in, 584.
Cholelithiasis, pathochemistry of liver in, 655.
Cholera, metabolism in, 147.
Cholesterol, chemistry of, 649.
Cholesterol content of blood, in nephritis, 342.
— in pregnancy, 858.
Cholin, as cause of nephritic toxicosis, 396.
Chyluria, 340.
Circulation, diseases of respiration and, see Respiration and Circulation, diseases of.
— in obesity, 34.
Circulatory system, in infantile diarrhea, 794.
— physiology of, in undernutrition, 19.
Coefficient of urea excretion, 357.
— Ambard's, 358.
— Austin, Stillman and Van Slyke, 360.
— clinical value of, 362.
— for estimating power of kidney to eliminate urea, 357.
— McLean's, 359.
— method of determining, 362.
— reliability of, 362.
Colchicum, in treatment of gout, 453.
Colloids, hydrophilic action of, 186.
Combined uric acid theory of gout, 442.
Concentration and dilution test for renal function, 381.
— table, 382.
Condensed milk, edema due to, 804.
Conductivity, of edema fluids, 162.
Consanguinity, and alkaptonuria, 502.
Constipation, metabolic complications of, 632.
Contracted kidney, primary, and essential hypertension, 400.

Contracted kidney, secondary, 399.
Creatin, as causative agent of uremia, 390.
— and oxalic acid, 464.
— in nephritis, 327.
Cretin dwarf, metabolism of, table, 828.
Creatinin, as causative agent of uremia, 390.
— in nephritis, 326.
— — comparative value of uric acid, urea and, in blood, 330.
Creatinin excretion in urine, in fasting, 14.
Creatinin nitrogen, in blood, in pregnancy, 855.
Creatinuria, in progressive muscular dystrophy, 723.
— with alkalosis, 724.
Creatorrhea, 664, 665.
— clinical occurrence of, 678.
Cretinism, see Infantilism.
Cyclic vomiting of children, acidosis in, cause of, 92.
— — diagnosis of, 92.
— — therapy for, 92.
— — type of, 92.
Cysteic acid, formula for, 518.
Cystin, action on, of bacteria, 531.
— analysis of, 515.
— chemistry of, 515.
— copper, 522.
— decomposition of, rôle of bacteria in, 521.
— derivation of, 517.
— detection and separation of, from urine, 522.
— as a disulphid, 517.
— excretion of, in urine, from subcutaneous injection of, 530, 532.
— feeding of, to dog, table of, 527, 528.
— — to dogs and rabbits, Blum's observations and tables, 532.
— — oxidation of, in urine, 530.
— formulæ for, 516.
— formula for cysteic acid, 518.
— identification of, obtained from stones and from protein decomposition, 521.
—insolubility of, in water, 522.
— nitrogenous substances present with, in urine, 525.
— occurrence of, in parts of body, 520.
— occurrence of, in protein molecule, 518.
— — in substances rich in keratin, 519.
— oxidation of, 518, 522.
— as precurser of taurin, 518.
Cystin, reactions of, 531.
— reduction of, 516.
— sulphur in, 515.
— synthesis of, 520.
Cystin calculi, 468.
Cystin fraction, quantitative analyses of, 518, 519.
Cystin nitrogen, determination of, in proteins, 519.
Cystinuria, amount of cystin excreted in, table, 526.
— cases of, in same family, 527.
— — Niemann's list, according to sex and age, 524.
— cause of, 523.
— cystin : nitrogen ratio, 529.
— and diaminuria, relation of, 479.
— due to defect in intermediary metabolism of amino-acid, 526.
— excretion of diamins in urine in, 479.
— leucin and tyrosin in urine of, 527.
— metabolic anomalies in, 535.
— metabolic changes in, 525.
— metabolic studies of, 527.
— nitrogen metabolism in, 527.
— rheumatic diatheses in, 529.
— sulphur partition in, 534.
— treatment of, 538.
— types of, 530.
— urine of, amino acids in, 527.
— Wolf's observations and tables on, 535, 537.

Dercum's disease, 40.
Dermatitis, associated with miscellaneous causes, 704.
Dermatitis exfoliativa, associated with miscellaneous causes, 704.
Dermatitis herpetiformis, associated with miscellaneous causes, 704.
Dermatoses, associated, with carbohydrate metabolism, 703.
— — with cardiovascular disease, 699.
— — with diet, 697.
— — — acne vulgaris, 698.
— — — angioneurotic edema, 698.
— — — eczema, 697.
— — — prurigo, 698.
— — — rosacea, 698.
— — — urticaria, 698.
— — with digestive disturbances, 695.
— — — acne vulgaris, 696.
— — — angioneurotic edema, 697.
— — — eczema, adult form of, 696.
— — — pruritus, 697.
— — — urticaria, 697.

Dermatoses, associated, with disturbed nitrogen metabolism, 702.
——with endocrin disturbances, 701.
——with miscellaneous causes, 703.
————acne or acne vulgaris, 704.
————acroasphyxia, 704.
————dermatitis, 704.
————dermatitis exfoliativa, 704.
————dermatitis herpetiformis, 704.
————erythema multiforme, 704.
————furunculosis, 705
————gangrenes, 705.
————pemphigus, 705.
————prurigo, 705.
————psoriasis, 705.
————rosacea, 705.
————seborrhea, 703, 705.
————urticaria, 705.
————xanthoma, 703, 705.
——with nervous diseases, 700.
——with renal disease, 700.
——with respiratory diseases, 701.
—relation of, to metabolic disturbances, 693.
————associated with carbohydrate metabolism, 703.
——————with cardiovascular disease, 699.
——————with disturbed nitrogen metabolism, 702.
——————with endocrin disturbances, 701.
——————with miscellaneous causes, 703.
————with nervous diseases, 700.
————with renal disease, 700.
————with respiratory diseases, 701.
————in diet, 697.
————in digestive disturbances, 695.
Diabetes, and acidosis, 277.
—Allen method of starvation in, 26.
—dietetic management of, 280.
——dealing with food supply in terms of carbohydrate, protein and fat, 283.
——discussion of hypothetical diets, 284.
——endogenous factors of food supply, 281.
——estimation of "optimal" caloric diets, 285.
——rationale of, 281.
——remarks on, 286.
—glucose in, cause of under consumption of, 273.
——impaired utilization of, cause of, 275.
—introduction to, 263.
Diabetes, metabolism in, total, 269.
—nature of internal secretion of pancreas, 276.
—relation of, to obesity, 36.
Diabetes insipidus, diagnosis of, 875.
—differential diagnosis of, 876.
—etiology of, 861.
——age, 863.
—classification of, 861.
—definition of, 861.
—etiology of, heredity, 864.
——infectious diseases, 865.
——new growths, 864.
——pregnancy, 866.
——sex, 863.
——syphilis, 866.
——trauma, 865.
—historical, 861.
—pathological anatomy of, 872.
—prevalence of, 862.
—prognosis of, 875.
—and sella turcica, 870.
—symptoms and signs of, amount of urine passed, 867.
——blood pressure, 867.
——blood sugar tests, 868.
——in carbohydrate metabolism, 867.
——in the hair, 867.
——mental, 867.
——optic, 869.
——polyuria and thirst, 867.
——sexual, 870.
——specific gravity of blood, 868.
——sweat glands, 867.
——temperature, 867.
—treatment of, 877.
——by lumbar puncture, 877.
——by pituitrin, 877.
Diabetic acidosis, clinical conditions in, comparison of, with results of different tests for clinical deficit, table, 85.
—diagnosis of, 88.
—therapy for, 89.
—type and cause of, 88.
Diabetic glycosuria, 267, 268.
Diabetic urine, heptose in, 304.
—sugars other than glucose in, 267.
Diamino acids, and diamins, relation between, 480.
Diamins, and diamino acids, relation between, 480.
—excreted in urine, in cystinuria, 479.
—origin of, Brieger's demonstration of, 480.
Diaminuria, and cystinuria, relation of, 477.
—significance of, 482.

Diarrhea, infantile, acidosis in, diagnosis of, 91.
——— therapy for, 92.
——— type and cause of, 90.
—— blood in, 793.
—— due to excess of fat, 789, 791.
——— to excess of food elements, 789.
—— feeding of cow's milk or cow's milk whey in, effects of, 795.
—— functional alterations in circulatory system, 794.
—— loss of organic constituents of food by the bowels, 792, 793.
—— metabolism in, 788.
—— process of, 794.
—— rôle of intestinal bacteria in, 790, 791.
—— rôle of organic acids in, 790.
—— symptoms of, 788, 789.
—— toxins in, theory of, 796.
—— urine in, 793.
—— water deficit in, accountable for symptoms, 796, 797.
—— weight loss in, explanation of, 796.
— metabolism of, in Addison's disease, 640.
—— in exophthalmic goiter, 640.
Diet, in blood diseases, influence of, on metabolism, 594.
— consisting solely of cereal grains, failure of, in proper nutrition, 244.
— deficiencies of, inorganic, 244.
— deficient, causing edema, 158.
—— experimental results of, on growth and nutrition, 243.
—— and pellagra, 900.
— deficient calcium, 246.
— disturbances of bone metabolism due to, 764.
— deficient protein, 246.
— dermatoses associated with, 697.
—— acne vulgaris, 698.
—— angioneurotic edema, 698.
—— eczema, 697.
—— prurigo, 698.
—— rosacea, 698.
—— urticaria, 698.
— in gout, 442.
—— acute form, 444.
—— chronic form, 445.
— influence of, on metabolism, in treatment of blood diseases, 594.
— influence of variations in, on metabolism in gastric disorders, 609.
— metabolic disturbances in infancy due to insufficiency of certain elements in, 802.
Diet, metabolic disturbances in infancy due to insufficiency of carbohydrates, 804.
—— edema, 802, 803.
—— of mineral salts, 805.
—— of proteins, 804.
—— of vitamines, 806.
— purin-free, for uric acid calculi, 469.
— in treatment of obesity, 47.
Diet factors in building up of hemoglobin, 559.
Diet scheme in oxaluria, 471.
Dietary for test day for renal function, 369.
Dietetic management of diabetes, 280.
— dealing with food supply in terms of carbohydrate, protein and fat, 283.
— discussion of hypothetical diets, 284.
— endogenous factors of food supply, 281.
— estimation of "optimal" caloric diets, 285.
— rationale of, 281.
— remarks on, 286.
Dietetic treatment of calculi, cystin, 472.
—— oxalate, 470.
—— phosphate, 468.
—— uric acid, 468.
—— xanthin, 472.
— of edema, 190.
—— Epstein's dietetic therapy of nephritis with edema, 191.
—— Karell régime, 190.
—— restriction of fluid and salt intake, 190.
Diets, nitrogen hunger of Landergren, 148.
— successful in nutrition, three types of, 245.
Diffusion pressure, in lymph production and edema, 183.
—— of the solute, 184.
—— of the solvent, 184.
Digestion, gastric, physiology of, 608.
Digestive canal, resorption of oxalate in, 463.
Digestive disturbances, dermatoses associated with, 695.
—— acne vulgaris, 696.
—— angioneurotic edema, 697.
—— eczema, adult form of, 696.
—— pruritus, 697.
—— urticaria, 697.
Digestive products, of Bence-Jones protein, 486.

Digestive system, physiology of, in undernutrition, 18.
Digitalis, in treatment of edema, 192.
Dilatation of the stomach, metabolism in, 622.
Diuretics, in treatment of edema, 192.
Ductless glands, abnormality of, metabolism in intestinal disturbances following, 640.
Drugs, in treatment of edema, digitalis, 192.
—— diuretics, 192.
—— purgatives, 193.
Duodenal contents, pancreatic ferments in, testing for presence of, 664.
Dyspnea, in nephritis, 312.

Eclampsia, and albuminuria, 835.
— and liver involvement, 836.
— metabolism in, table, 851.
—— tables of, 844, 845.
— theories of cause of, 838.
Eczema, adult form of, associated with digestive disturbances, 696.
— associated with diet, 697.
— etiological division into groups, 696.
— in infancy and early childhood, metabolism in, 809.
Edema, anatomy of, morbid, 159.
— angioneurotic, 158.
— blood flow in, rate and volume of, 170.
— blood and plasma volume in, 170.
— blood serum analysis in sodium bicarbonate, form of, 167.
— of the brain and nephritic toxicosis, 394.
— in cachexia, 158.
— capillary permeability and, 169.
— causes of, chemical, 158.
—— dietary deficiency, 158.
—— heredity, 159.
—— mechanical, 157.
—— neuropathic, 158.
—— protein poisoning, 158.
— and cell metabolism, 66.
— and cell respiration, 166.
— chemistry of fluids of, 159.
—— analyses of blood and edema fluid in, war-edema, 168.
—— average composition of effusion fluids, table, 161
—— blood serum analysis in sodium bicarbonate, form of, 167.
—— chemical characteristics of transudates, table, 164.
—— chlorid content, 162.
Edema, chemistry of fluids of, chlorid content, table, 163.
—— composition of cutaneous effusions, 161.
—— concentration of electrolysis, 162.
—— conductivity, 162.
—— enzymes of the plasma, 164.
—— freezing point, 162.
———— table, 163.
—— immune bodies, 164.
—— molecular concentration, 162.
—— non-protein constituents, 161.
———— table, 162.
—— non-protein nitrogen content of, table, 163.
—— protein constituents, 160.
—— reaction of, 164.
—— review of chemistry of normal lymph, 160.
—— sugar, 162.
—— surface tension, 164.
—— toxicity, 165.
— circulatory changes and, 170.
—— blood and plasma volume in, 170.
—— composition of blood in heart failure, 172.
—— rate and volume of blood flow, 170.
— clinical features of, ascites, 157.
—— general, 156.
—— hydrothorax, 157.
—— kidneys, 157.
—— in the liver, 157.
—— lungs, 157.
—— skin and subcutaneous tissues, 156.
— composition of blood in heart failure, 172.
—— carbon dioxid content, 172.
—— oxygen content, 172.
—— number and volume of red cells, 173.
—— reaction of blood, 173.
—— sodium chlorid content of plasma, 173.
—— summary, 174.
— cutaneous effusions of, chemical composition of, 161.
— definition of, 153.
— definition of terms relative to, 165.
— famine, 158.
— fluids of, chemistry of, 159. See also Chemistry of fluids of.
— forms of, 157.
—— general manifestations of, 157.
— of heart failure, composition of blood in, 172.
———— carbon dioxid content, 172.

Edema, of heart failure, composition of blood in, oxygen content, 172.
———number and volume of red cells, 173.
———reaction of blood, 173.
———sodium chlorid content of plasma, 173.
———summary, 174.
——hydrothorax of, 157.
——skin and subcutaneous tissues in, 156.
——treatment of, 189.
—hereditary, chronic, 159.
—historical, 153.
—in inanition, 158.
—in infancy and early childhood, due to condensed milk, 804.
——due to insufficiency of certain elements in diet, 802, 803.
——pathogenesis of, theories as to, 804.
—inflammatory, 159.
—influence of chlorids and fluids, 187.
—and inorganic metabolism, 166.
—introduction to, 153.
—of the kidneys, 157.
—of the liver, 157.
—of the lungs, 157.
—lymph production, 179.
——physico-chemical factors in, 181.
———diffusion pressure, 183.
————of the solute, 184.
————of the solvent, 184.
———electrostatic pressure, 187.
———hydrophilic action of colloids, 186.
———hydrostatic pressure, 181.
———osmotic pressure, 184.
—morbid anatomy of, 159.
—morphology and chemical pathology of, chemistry of edema fluids, 160.
——morbid anatomy of, 159.
—nature of, 180.
—in nephritis, 312.
——treatment of, 189.
———Epstein's dietetic therapy, 191.
—neuropathic, 158.
—pathological physiology of, 165.
——analyses of blood and edema fluid in war edema, 168.
——blood serum analysis in sodium bicarbonate edema, 167.
——capillary permeability, 169.
——cell metabolism and edema, 166.
——cell respiration and, 166.
Edema, pathological physiology of, circulatory changes, 170.
——definition of terms used in discussion, 165.
——disturbances in flow of lymph, 165.
——inorganic metabolism, and, 166.
——protein metabolism and, 166.
——renal excretory function in its relation to, 174.
——rôle of thyroid ink, 167.
—physico-chemical factors in, 181.
——diffusion pressure, 183.
———electrostatic pressure, 187.
———of the solute, 184.
———of the solvent, 184.
——hydrophilic action of colloids, 186.
——hydrostatic pressure, 181.
——osmotic pressure, 184.
—from the physico-chemical standpoint, 179.
——nature of edema, 180.
——physico-chemical factors in lymph production and edema, 181.
———diffusion pressure, 183.
————of the solute, 184.
————of the solvent, 184.
———electrostatic pressure, 187.
———hydrophilic action of colloids, 186.
———hydrostatic pressure, 181.
———osmotic pressure, 184.
—problem of, 155.
—and protein metabolism, 166.
—renal excretory function in its relation to, 174.
——nephritis, acute diffuse, 175.
———chronic diffuse, 176.
———chronic interstitial, 175.
———chronic parenchymatous, 176.
———subacute, 176.
——renal function in other conditions associated with edema, 178.
——summary of, 178.
—soda, 158.
—sodium bicarbonate, blood serum analysis in, 167.
—spontaneous, 158.
—and thyroid gland, rôle of, 167.
—treatment of, baths, 194.
——dietetic, 190.
———Epstein's dietetic therapy of nephritis with edema, 191.
———Karell régime, 190.
———restriction of fluid and salt intake, 190.
——drug therapy, digitalis, 192.

Edema, treatment of, drug therapy, diuretics, 192.
———purgatives, 193.
———thyroid extract, 193.
——of edema of heart failure, 189.
——etiologic, 189.
——in nephritis, 189.
——prophylaxis, 188.
—war, 158.
——analyses of blood and edema fluid in, 168.
Electrostatic pressure, in lymph production and edema, 187.
Endocrin disturbances, dermatoses associated with, 701.
Endocrin therapy, for edema, thyroid extract, 193.
Energy, source of, for muscular contraction, 709.
———glucose supply, 715.
———oxygen supply, 709.
Energy metabolism, in undernutrition, body temperature, 7.
———tables, 8.
——heat production, 8.
Energy requirements of body, on account of work performed, 33.
—basal metabolism, 31.
—effect of food on metabolism, 33.
—Meeh formula for determining surface area, 31.
Enteritis, metabolism in, 629.
Enteropathies, congenital, metabolism in, 636.
—due to alterations of lumen or position of intestines, metabolism in, 633.
—inflammatory, metabolism in, 629.
—neoplastic, metabolism in, 638.
—nervous, metabolism in, 637.
—parasitic, metabolism in, 635.
Enteroptosis, metabolism in, 635.
Enzymes of the plasma, in edema fluids, 164.
Epilepsy, starvation in, therapeutic use of, 27.
Epinephrin, as cause of arterial hypertension in nephritis, 404.
Erysipelas, metabolism in, 138.
——analyses of blood and urine, 139.
——respiratory, 139.
——total, 138.
Erythema multiforme, associated with miscellaneous causes, 704.
Excretory system, effect on, of undernutrition or fasting, 21.
Exercise, in treatment of obesity, 47.
Exophthalmic goiter, diarrhea of, metabolism in, 640.
Experimental fever in animals, metabolism in, 150.
Exudative diathesis, in infancy and early childhood, metabolism in, 809.

Famine edema, 158.
Fasting, body weight in, 16.
——percentage loss in weight of various organs in starvation, table, 18.
—breaking fast, 25.
—carbohydrate metabolism in, 10.
—cause of death from, 25.
—chlorin balance in, table, 15.
—creatinin excretion in, 14.
—effect of, on circulatory system, 19.
——on digestive system, 18.
——on excretory system, 21.
——on kidneys, 21.
——on mental balance and disposition, 22.
——on mental capacity, 22.
——on muscular system, 17.
——on nervous system, 21.
——on reproductive system, 23.
——on respiration, 21.
—fat metabolism in, 10.
—mineral metabolism in, 15.
—nitrogen excreted in urine in, 13.
—possible duration of, 24.
—protein metabolism in, 12.
—pulse rate in, 20.
—sulphur excretion in, 14.
—in therapeutics, 26.
——Allen method of starvation, in diabetes, 26.
——epilepsy, 27.
——in gastrointestinal disturbances, 26.
——obesity, 27.
—voluntary, 4.
—water balance in, 6.
—See also Starvation; and Undernutrition.
Fasting cure, 26.
Fat, in bile, 649.
—in the feces, forms of, 679.
——in infantilism, 820.
——in pancreatic disease, see Stools, in pancreatic disease.
—in food supply of diabetes, 283.
—and nitrogen excretion, in calculous cirrhosis of pancreas, 671.
——in malignant tumors of the pancreas, 671.
——with pancreatic duct closed, 669.
——in pancreatitis, acute, 669.

Fat, and nitrogen excretion, in pancreatitis, chronic, 670.
— as source of glucose supply, 272.
Fat metabolism, effect on, of oxygen-lack, 544.
— in nephritic, analyses of Bloor, table, 341.
— — blood lipoids, 341.
— — cholesterol content of blood, 342.
— — lipemia, 342.
— — lipuria (chyluria), 340.
— — utilization of fat, 340.
— in typhoid fever, 109.
— in undernutrition, 10.
"Fat necrosis" of the pancreas, 684.
— toxic element in, 688.
Fatty acids, and the liver, 644.
Fatty infiltration, in progressive muscular dystrophy, 726.
Fatty stool, in pancreatic disease, 664, 665.
Fecal matter, fractional composition of, in pancreatic disease, 679.
Feces, fat in, in infantilism, 820.
— muscle fiber in, in pancreatic disease (creatorrhea), 664, 665.
— nitrogen in, in infantilism tables, 818.
— nitrogen in urine and, in infantilism, tables, 817, 819.
Ferment theory of gout, 442.
Fetus, in puerperal osteomalacia, 757.
Fever, metabolism in, 95.
— — basal, and Van't Hoff's law, 121.
— — cholera, 147.
— — erysipelas, 138.
— — experimental fever in animals, 150.
— — fever caused by parenteral injection of foreign proteins, 144.
— — infectious diseases, 148.
— — malarial fever, 140.
— — observations on, 149, 150.
— — pneumonia, lobar, 124.
— — rheumatic fever, acute, 149.
— — scarlet fever, 148.
— — syphilis, 148.
— — toxic and non-toxic, compared, 149.
— — tuberculosis, 131.
— — typhoid fever, 96.
— — Van't Hoff's law, 121.
Food, constituents of, necessary for nutrition, 239.
— effect of, on metabolism, 33.
— — in tuberculosis, 135.
— — in typhoid fever, 116.
Food, purin-containing, effect of, on output of uric acid, 423.
— required to bring typhoid patients into nitrogen equilibrium, 116.
— in typhoid fever, specific dynamic action of, 118.
Food absorption, theory of an internal secretion of the pancreas controlling, 675.
Food products, influence of, on blood pressure, 406.
Food shortage, and bone metabolism, 769.
Food supply, in diabetes, dealing with, in terms of carbohydrate, protein and fat, 283.
— — endogenous factors of, 281.
Foodstuffs, character of, oxidized in malarial fever, 143.
— oxidized in tuberculosis, character of, 134.
Fragmentation, in process of blood destruction and regeneration, 555.
Free acid and ammonia, determination of excretion of, 83.
Fructose, concentration of, in the blood, 299.
— — in urine, 298.
— recognition of, 296.
Fructose tolerance, test for hepatic function, 300.
Fructosuria, occurrence of, 297.
— significance of, 299.
— treatment of, 299.
Furunculosis, associated with miscellaneous causes, 705.

Galactosuria, occurrence of, 301.
— pathognomonic factors in, 301.
— recognition of, 302.
Gangrenes, associated with miscellaneous causes, 705.
Gaseous exchange, in diseases of respiration and circulation, 545.
Gastric carcinoma, metabolism in, 619.
Gastric digestion, physiology of, 608.
Gastric diseases, metabolism in, 607.
— — atony, 622.
— — carcinoma, 619.
— — dilatation, 622.
— — gastric erosions, 618.
— — gastric neuroses, 622.
— — gastric ulcer, 618.
— — gastritis, 618.
— — gastroptosis, 621.
— — influence of variations in diet, 609.

Gastric diseases, metabolism in, influence of variations in secretory and motor functions, 610.
— — influence on, of vitamines, 610.
— — intestinal disturbances secondary to, 639.
— — lues, 621.
— — motor disturbances, 614.
— — — hypermotility, 615.
— — — motor insufficiency, 615.
— — — vomiting, 614.
— — physiology of gastric digestion, 608.
— — polyposis, 621.
— — pylorospasm, 618.
— — secretory disturbances, 611.
— — — hyperacidity, hyperchlorhydria, hypersecretion, 611.
— — — hyposecretion, hypochlorhydria, subacidity, achlorhydria, achylia, 612.
Gastric disturbances of other diseases, metabolism in, 623.
Gastric erosions, metabolism in, 618.
Gastric lues, metabolism in, 621.
Gastric neuroses, metabolism in, 622.
Gastric operations, metabolism in, 623.
Gastric polyposis, metabolism in, 621.
Gastric ulcer, metabolism in, 618.
Gastritis, metabolism in, 618.
Gastro-intestinal canal, fundamental function of, 607.
Gastro-intestinal disturbances, fasting therapy in, 26.
Gastro-intestinal tract, effect on, of anaphylaxis, 202.
Gastroptosis, metabolism in, 621.
Genital origin of obesity, 39.
— metabolism in, 46.
Glaucoma, cause of, 158.
Glucose, amount of, in blood, normally, 716, 717.
— — in pathological conditions, tables, 717.
— — under general activity, 718.
— concentration of, in blood, 716, 718.
— — organs controlling, 718.
— glycuronic acid derived from, 305.
— delayed utilization, in progressive muscular dystrophy, 725.
— excretion of, in fasting, 266.
— — total, 265.
— impaired utilization of, in diabetes, 275.
— in muscular atrophy, secondary to chronic arthritis, 722.
— osteomalacia induced by injection of, 768.
Glucose, in progressive muscular dystrophy, table, 721.
— supply, influence of, on muscle power, 715.
— underconsumption of, in diabetes, cause of, 273.
— supply of, deductions on, 273.
— — sources of, carbohydrates, 270.
— — — protein, 271.
— — — fat, 272.
— supply and excretion of, 268.
Glucose curve, 265.
— in diabetic glycosuria, 268.
Glucose metabolism, 306.
— disturbances of, glycosuria, 306.
— — hyperglycemia, 306.
Glycocoll, in gout, 440.
Glycosuria, definition of, 264.
— diabetic, 267, 268.
— — mechanism of, 268.
— as disturbed glucose metabolism, 306.
— glucose curve, 265.
— mechanism of, 268.
— — diabetic, 268.
— normal and abnormal, 264, 266.
— in pregnancy, 857.
Glycosuric acid, in urine of alkaptonurics, 503.
Glycuronic acid, Cammidge reaction, 305.
— derived from glucose, 305.
Gout, action in, of phenylcinchoninic acid (atophan, cinchophan), 438.
— acute, treatment of, 444.
— chronic, treatment of, 445.
— deposition of sodium monourate in, 439.
— diet in, 442.
— — in acute form, 444.
— — in chronic form, 445.
— gastric disturbances in, and metabolism, 623.
— glycocoll in, 440.
— metabolism in, general, 440.
— — introduction to, 411.
— — and purin bodies, 412.
— nature of, 411.
— relation of, to obesity, 36.
— theories of, combined uric acid theory, 442.
— — ferment, 442.
— — renal, 441.
— — tissue retention, 442.
— treatment of, atophan therapy, 448.
— — baths, 454.
— — by colchicum, 453.
— — diet, 442.

Gout, treatment of, diet, in acute form, 444.
— — — in chronic form, 445.
— — — table of foods with their percentage of purin-nitrogen and uric acid precursors from estimations by Walker Hall, 455.
— — exercise, 454.
— — by morphin, 453.
— — radium emanations, 454.
— — by salicylates, 454.
— — spas and springs, 455.
— uric acid of, 411.
— — in blood, 428.
— — in joint exudates, 434.
— — and purin bodies, 412.
— — in tissues, 435.
— urine in, 436.
Growth, changes in, due to deficient calcium in diet, 246.
Growth, definite laws followed by, 240.
— disturbances of, 241.
— — due to lack of sufficient food, 242.
— — faulty diets, 242.
— — and vitamines, 242.
— effects of undernutrition, 247.
— — Aron's experiments, 247.
— — other observations on, 248.
— experimental observations of effects on, of deficient diets, 243.
— ideal in nutrition during period of, 242.
— interference with, by deficient protein in diet, 246.
— mechanism of, 241.
— requirements of, 239.
— — food constituents, 239.
— and vitamines, 242.
Guanin, formula for, 414.

Heart, effect on, of anaphylaxis, 202.
Heart failure, edema of, composition of blood in, 172.
— — hydrothorax in, 157.
— — skin and subcutaneous tissues in, 156.
— — treatment of, 189.
Heat production, in undernutrition, 8.
Heat regulation in anaphylaxis, 213.
Hemoglobin, breaking down of, 558.
— — rate of, methods of determining, 561.
— building up of, 559.
— — diet factors in, 559.
— — liver cell activity in, 559.
Hemoglobin pigment metabolism, breaking down of hemoglobin, regulatory function of liver in bile-pigment metabolism, 558.
— building up of hemoglobin, liver cell activity and diet factors, 559.
— — methods of determining rate of hemoglobin destruction, 561.
— regulatory influence of spleen in blood formation and destruction, 562.
Hemolytic anemia, iron metabolism in, 588.
— nitrogen partition in, 584.
— purin metabolism in, 580.
Hemolytic process, in blood destruction and regeneration, 555.
Hemorrhage, metabolism in, iron, 586.
Hepatic disease, leucin in urine in, 476.
— tyrosin in urine in, 476.
Hepatic function, fructose tolerance test, 300.
Hepatic toxemia, metabolism in, table, 853.
Heptose, in diabetic urine, 304.
Heptosuria, 304.
Heredity, as factor in diabetes insipidus, 864.
— — in obesity, 34.
Hirschsprung's disease, metabolism in, 636.
Homogentisic acid, formation of, a pathological process, 510.
— in urine of alkaptonurics, 503.
— amount excreted, 511.
— — formula for, 504.
— — synthesis of, Baumann and Frankel, 504.
— — — Osborne, 505.
— — — Neubauer and Falta, 506.
— — transformation of tyrosin to, 507.
Hourglass stomach, metabolism in, 618.
Hydrogen ion concentration of blood plasma and other extracellular fluids, 54.
Hydrophilic action of colloids, 186.
Hydrostatic pressure, in lymph production and edema, 181.
Hydrothorax, of edema, 157.
Hyperacidity, metabolism in, 611.
Hyperchlorhydria, metabolism in, 611.
Hyperglycemia, as disturbed glucose metabolism, 306.
Hypermotility, metabolism in, 615.
Hyperthyroidism, gastric disturbances in, and metabolism, 623.
Hypochlorhydria, metabolism in, 612.

Hypocholesterinemia, in progressive muscular dystrophy, 724.
— — delayed glucose utilization, 725.
— — fatty infiltration, 726.
Hypochylia pancreatica, metabolism in, 674.
Hypoglycemia, in progressive muscular dystrophy, 720.
— — with alkalosis, 724.
Hypophyseal obesity, 37.
— metabolism in, 44.
Hypophysis, relation between disturbances of bone metabolism and, 767.
Hyposecretion, metabolism in, 612.
— of stomach, metabolism in, 611.
Hyposthenuria, 335.
Hypoxanthin, formula for, 413.

Immune bodies, in edema fluids, 164.
Inanition, edema in, 158.
Indicanemia, as causative agent of uremia, 391.
Infancy and early childhood, metabolism in, 781.
— — in athreptic infants, 799.
— — disturbances due to diminished capacity of certain organ systems, 806.
— — disturbances due to an excessive intake of food, alkaline condition of intestines, 784.
— — — breast milk, 788.
— — — Czerny's classification, 783.
— — — excess of protein, 786, 787.
— — — general symptoms, 783.
— — — infantile diarrhea, 788.
— — — mineral metabolism, 785.
— — — pathogenesis, 783, 786.
— — — relationship between amount and quality of food and of weight, 782.
— — — stools in, alkaline, 784.
— — — — "soap," 783, 785.
— — — symptoms coincident with variations in weight curve, 782.
— — disturbances due to insufficiency of certain elements in diet, 802.
— — — deficiency of carbohydrates, 804.
— — — deficiency of protein, 804.
— — — edema, 802, 803.
— — — mineral salts, 805.
— — — vitamines, 806.
— — disturbances due to insufficient intake of food, 798.
— — exudative diathesis (eczema), 809.
— — in infantile diarrhea, 788.
Infancy and early childhood, metabolism in, tetany or spasmophilia, 806.
Infantile diarrhea, blood in, 793.
— due to excess of fat, 789, 791.
— — excess of food elements, 789.
— feeding of cow's milk or cow's milk whey in, effects of, 795.
— functional alterations in circulatory system, 794.
— loss of organic constituents of food by the bowels, 792, 793.
— metabolism in, 788.
— process of, 794.
— rôle of intestinal bacteria in, 790, 791.
— rôle of organic acids in, 790.
— symptoms of, 788, 789.
— toxins in, theory of, 796.
— urine in, 793.
— water deficit in, accountable for symptoms, 796, 797.
— weight loss in, explanation of, 796.
Infantilism, bone fragility in, 820.
— causes of, 813.
— classification of, 813.
— intestinal, 814.
— metabolism in, achondroplasiac dwarf, table, 827.
— — and bone fragility, 820.
— — cretin dwarf, table, 828.
— — dwarf, type of Lorraine, 826.
— — fat, 819.
— — fat in the feces, 820.
— — fatty acids, table, 831.
— — intestinal form, after partial improvement, table, 830.
— — intestinal infantilism, 814.
— — introduction to, 813.
— — mineral, 820.
— — — calcium, 820, 824.
— — — — table, 831.
— — — magnesium, 825.
— — — — table, 831.
— — — phosphate, 825.
— — — — table, 831.
— — — ratios, 826.
— — — summary, 827.
— — nitrogen in the feces, table, 818.
— — nitrogen in the feces and urine, table, 817, 819.
— — nitrogen in the urine and feces, tables, 817, 819.
— — nitrogen and sulphur distribution in urine, 814.
— — — tables, 815, 816.
— — tables, 824, 825.
— pancreatic, 681.

Infants, athreptic, metabolism in, 799.
Infection, arthropathies secondary to, metabolism in, 773.
Infectious diseases, as cause of diabetes insipidus, 865.
— miscellaneous, metabolism in, 148.
Inflammatory edema, 159.
Inflammatory enteropathies, metabolism in, 629.
Inorganic metabolism, and edema, 166.
Inorganic salts, metabolism of, in diseases of respiration and circulation, 551.
Intestinal bacteria, rôle of, in infantile diarrhea, 790, 791.
Intestinal bacterial origin of alkapton, objections to, 508.
Intestinal carcinoma, metabolism in, 638.
Intestinal chyme, constituents of, 626.
Intestinal diseases, metabolism in, Addison's diseases, diarrhea of, 640.
— — anchylostomiasis, 636.
— — appendicitis, 631.
— — carcinoma, 638.
— — constipation, 632.
— — diarrhea of Addison's disease, 640.
— — diarrhea of exophthalmic goiter, 640.
— — disturbances of motor innervation, 637.
— — disturbances of secretory innervation, 637.
— — disturbances of sensibility, 637.
— — enteritis, acute and chronic, 629.
— — enteropathies, congenital, 636.
— — — due to alterations of lumen or of position of intestines, 633.
— — — neoplastic, 638.
— — — parasitic, 635.
— — enteroptosis, 635.
— — exophthalmic goiter, diarrhea of, 640.
— — following abnormality of ductless glands, 640.
— — functions of intestines, 625.
— — — absorptive, 628.
— — — motor, 627.
— — — secretory, 626.
— — inflammatory enteropathies, 629.
— — intestinal chyme, 626.
— — introduction to, 624.
— — lymphosarcoma, 638.
— — mechanical factors, 625.
— — motor processes, 627.
Intestinal diseases, metabolism in, obstruction, acute and chronic, 633.
— — perforated ulcer, 631.
— — physiological processes of intestines, 624.
— — polyposis intestinalis, 638.
— — sarcoma, 638.
— — when secondary to diseases of stomach, 639.
— — secretory processes, 626.
— — specific, 639.
— — syphilis, 639.
— — teniasis, 636.
— — tuberculosis, 639.
— — ulceration of intestines, 630.
— — uncinariasis, 636.
Intestinal disturbances, secondary to diseases of stomach, metabolism in, 639.
Intestinal infantilism, 814.
Intestinal lymphosarcoma, metabolism in, 638.
Intestinal malposition, congenital, metabolism in, 636.
Intestinal obstruction, auto-intoxication accompanying, 634.
— metabolism in, 633.
— symptoms of, 633.
Intestinal polyposis, metabolism in, 638.
Intestinal sarcoma, metabolism in, 638.
Intestinal syphilis, metabolism in, 639.
Intestinal tuberculosis, metabolism in, 639.
Intestinal ulceration, metabolism in, 630.
Intestines, functions of, 625.
— — absorptive, 628.
— — motor, 627.
— — secretory, 626.
— physiological processes of, 624.
Iron metabolism, in anemic and healthy individuals, table, 587.
— in blood diseases, 585.
— in chlorosis, 588.
— in hemolytic anemia, 588.
— in hemorrhage, 586.
— influence on, of spleen, 596.
— in leukemia, 589.

Jaundice, congenital hemolytic, metabolism in, after splenectomy, 600.
— — purin metabolism in, 581.
— liver functional tests in, 652.
— obstructive, causing decalcification of bones, 761.
— — concomitant to obstruction of pancreatic duct, 663.

Joint exudates, uric acid in, in gout, 434.
Joints, diseases of, see Arthropathies.
— metabolism in diseases of, 772.
— — arthropathies secondary to infections, 77.
— — classification of arthropathies, 772.
— — gout, 772.
— — primary atrophic arthritis, 773.
— — table showing results of observations on, 775, 776, 777.
— — primary hypertrophic arthritis, 773.
— — — table of nine-day observations on, 774.
— — trophic arthropathies secondary to disease of central nervous system, 772.
Kahler's disease, 498.
Karell's régime in edema, 190.
Kidney, contracted, primary, 400.
— — secondary, 399.
Kidney secretion, as cause of arterial hypertension in nephritis, 405.
Kidneys, in edema, 157.
— effect on, of fasting, 21.
— excretion of acid products by, 56, 65.
— in obesity, 35.

Lactic acid, presence of, in oxygen-lack, 543.
Lactose, osteomalacia induced by injection of, 768.
Lactose test for renal function, 357.
Lactosuria, occurrence of, 301.
— pathognomonic factors in, 301.
— recognition of, 302.
Leucin, in urine, conditions causing, 476.
— — in cystinuria, 527.
Leukemia, metabolism in, basal, 567.
— — — experimental and clinical observations, 567, 570.
— — — table of, 571.
— — high, causes of, 573.
— — influence on, of diet, 594.
— — influence on, of röntgen rays and radium, 601.
— — — of transfusion, 594.
— — mineral, iron, 589.
— — — phosphoric acid, calcium and magnesium, 590.
— — protein, 578.
— — purin, 579.
— — — elimination of uric acid and purin bases, 581.
Leukemia, nitrogen balance in, 578.
— treatment of, by diet, influence of, on metabolism, 594.
— — by röntgen-rays and radium, influence of, on metabolism, 601.
— — by transfusion, influence of, on metabolism, 594.
Lipemia, in nephritis, 342.
Lipodystrophia progressiva, 37.
Lipoids of the blood in nephritis, 341.
Lipomatosis, circumscribed nodular, 37.
— diffuse symmetrical, 37.
— distinguished from obesity, 36.
— lipodystrophia progressiva, 37.
Lipuria, 340.
Liver, and the carbohydrates, 643.
— chemistry of, normal, 643.
— — — bile, 647.
— — — — bile pigments, 648.
— — — — bile salts, 648.
— — — — bilirubin, 648.
— — — — cholesterol, 649.
— — — — fat, 649.
— — — — mineral substances, 649.
— — — detoxicating function, 646.
— — — liver and carbohydrates, 643.
— — — liver and fatty acids, 644.
— — — liver and proteins, 645.
— — — tests of liver function, 649.
— — in acute yellow atrophy, 654.
— detoxicating function of, 646.
— effect on, of anaphylaxis, 203.
— and the fatty acids, 644.
— functional tests of, in acute yellow atrophy, 653.
— — in disease, 651.
— — in jaundice, 652.
— in obesity, 35.
— — in cholelithiasis, 655.
— — composition of liver in acute yellow atrophy, 654.
— — functional tests in disease, 651.
— — — acute yellow atrophy, 653.
— — — jaundice, 652.
— and the proteins, 645.
— regulatory function of, in bile-pigment metabolism, 558.
— symptoms associated with, in edema, 157.
Liver cell activity and diet factors in building up of hemoglobin, 559.
Liver involvement, and eclampsia, 836.
Liver necrosis, experimental, urine in, 842.
Lues, gastric, metabolism in, 621.
Lumbar puncture, in treatment of diabetes insipidus, 877.

Lungs, edema of, 157.
— effect on, of anaphylaxis, 201.
— in obesity, 35.
Lymph, Bence-Jones protein in, 487.
— disturbances in flow of, 165.
— normal, chemistry of, 160.
Lymph production, 179.
— influence of chlorids and fluids, 187.
— physico-chemical factors in, 181.
— — diffusion pressure, 183.
— — — of the solute, 184.
— — — of the solvent, 184.
— — electrostatic pressure, 187.
— — hydrophilic action of colloids, 186.
— — hydrostatic pressure, 181.
— — osmotic pressure, 184.
Lymphosarcoma of the intestines, metabolism in, 638.

Magnesium, amount of, in bone, disproportionate increase of, in artificial osteomalacia, 741.
Magnesium metabolism, 460.
— in blood diseases, 589.
— in osteomalacia, 745.
Magnesium oxid, amount of, in bone ash, 740.
— — in dried bone, 740.
Magnesium phosphate, amount of, in bone ash, 740.
Malaria, temperature regulation in, 140.
Malarial fever, metabolism in, calorimetry, direct and indirect, 144.
— — chlorids and phosphates in, 144.
— — character of foodstuffs oxidized, 143.
— — temperature regulation, 141.
— — total, 140.
Malnutrition, borderline, 250, 251.
— experimental results of, 243.
Malposition of intestines, congenital, metabolism in, 636.
Maltose, in urine, diabetic and other, 303.
Maltosuria, 303.
McLean's coefficient of urea excretion, 359.
Meckel's diverticulum, metabolism in, 636.
Medicinal treatment of calculi, cystin, 472.
— — oxalate, 471.
— — phosphate, 468.
— — uric acid, 470.
— — xanthin, 472.
Meeh formula for determining surface area, 31.
Megacolon congenitum, metabolism in, 636.
Mental balance, effect on, of undernutrition and fasting, 22.
Mental capacity, effect on, of undernutrition and fasting, 22.
Metabolic changes, in cystinuria, 525.
Metabolic studies, in Bence-Jones protein, cases excreting, tables of Folin and Denis, 490, 491.
— — — — — Hopkins and Savory (multiple myeloma case), 492, 493.
— — — — — Hopkins and Savory (three different cases), 494, 495.
— — — — — of Seegelken (multiple myeloma), 495, 496.
— — — — — of Walters (multiple myeloma), 496, 497, 498.
— of renal calculi, calcium metabolism, 459.
— — cystin calculi, 468.
— — magnesium metabolism, 460.
— — oxaluria and oxalate calculi, 462.
— — phosphaturia and phosphate stones, 458.
— — phosphorus metabolism, 458.
— — uraturia and uric acid calculi, 465.
— — xanthin calculi, 467.
Metabolism, abnormal, Bence-Jones protein as a product of, 490.
— in anaphylaxis, asthma, 229.
— — heat regulation, 213.
— — protein, 209.
— — respiratory, 212.
— — urticaria, 229.
— anomalies of, in cystinuria, 535.
— basal, in anemia, 567.
— — in children, 32.
— — in fever, and Van't Hoff's law, 121.
— — formula for predicting in healthy adults, 32.
— — in leukemia, 567.
— — meaning of term, 31.
— — in pneumonia, lobar, 125.
— — in shock, 257.
— bile-pigment, regulatory function of liver in, 558.
— of blood and blood-forming organs, pathological, blood destruction and regeneration, mechanism of, 554.
— — — newer aspects of, 553.
— — — regulatory influence of spleen in, 562.

Metabolism, of blood and blood-forming organs, hemoglobin pigment metabolism, breaking down of hemoglobin, 558.
— — — building up of hemoglobin, 559.
— — — methods of determining rate of hemoglobin destruction, 561.
— — — regulatory influence of spleen in blood formation and destruction, 562.
— — introduction to, 553.
— in blood diseases, anemia, basal metabolism, 567.
— — — bothriocephalus, purin metabolism, 581.
— — — hemolytic, iron metabolism, 588.
— — — hemolytic, purin metabolism, 580.
— — — nitrogen balance, 574.
— — — protein metabolism, 574.
— — — purin metabolism, 579.
— — — secondary, basal, 568.
— — — — purin metabolism, 580.
— — — — table, 569.
— — chemical changes in nitrogenous metabolites and fats of blood, 592.
— — chlorosis, basal, 568.
— — — — table, 569.
— — — iron, 588.
— — — purin metabolism, 580.
— — hemorrhage, iron metabolism, 586.
— — influence on, of some measures of treatment, benzol, 604.
— — — diet, 594.
— — — röntgen-rays and radium, 601.
— — — splenectomy, 596.
— — — transfusion, 594.
— — jaundice, congenital hemolytic, purin metabolism, 581.
— — leukemia, basal metabolism, 567.
— — — — table, 571.
— — — iron metabolism, 589.
— — — protein metabolism, 578.
— — — purin metabolism, 579.
— — mineral, 585.
— — — iron, 585.
— — — phosphoric acid, calcium and magnesium, 589.
— — — sulphur, 591.
— — pernicious anemia, basal metabolism, 568.
— bone, abnormal, cause of, 752.
— — calcium, 738, 739.
— — in different stages of osteomalacia, 770, 771.
Metabolism, bone, effect on bone composition of calcium, magnesium and strontium content of diet, 742.
— — etiology of disturbances of, acromegaly, 761.
— — — adrenal glands, 766.
— — — arteriosclerosis, 761.
— — — calcareous metastases, 761.
— — — calcification of muscles and organs, 761.
— — — diet deficient in calcium, 764.
— — — divergence of nature of, 766.
— — — food shortage, 769.
— — — hypophysis cerebri, 767.
— — — obstructive jaundice, 761.
— — — osteomata and calcification of various tissues, 763.
— — — other than pregnancy and lactation, 761.
— — — oxalic acid or oxalates in food, 768.
— — — parathyroid glands, 767.
— — — renal stones, 761.
— — — thymus, 767.
— — — thyroid gland, 766.
— — — transmittable infectious agent in osteomalacia and rickets, 766.
— — — vitamines, 769.
— — magnesium, 739, 740.
— — normal, 735.
— — overproduction and bone disease, 769.
— — phosphate, 739.
— — ratio of Ca : Mg (normal and in osteomalacia), in bone ash, 741.
— — — in dried bone, 741.
— — sulphur percentage in dried bone, 743.
— calcium, 459.
— carbohydrate, dermatoses associated with disturbances of, 703.
— disturbances of, other than in diabetes, glycuronic acid, 305.
— — — fructosuria, 296.
— — — galactosuria, 301.
— — — heptosuria, 304.
— — — introduction to, 289.
— — — lactosuria, 301.
— — — maltosuria, 303.
— — — pentosuria, 292.
— — effect on, of oxygen-lack, 543.
— — in nephritis, 343.
— — in typhoid fever, 109.
— — in undernutrition, 10.
— cell, and edema, 166.
— chlorid, in pneumonia, lobar, 127.
— in cholera, 147.
— in diabetes, acidosis, 277.

Metabolism, in diabetes, cause of impaired glucose utilization, 275.
——cause of underconsumption of glucose, 273.
——dietetic management of, 280.
——nature of internal secretion of pancreas, 276.
——sources of glucose supply, carbohydrates, 270.
———fat, 272.
———protein, 271.
——total, 269.
—in diseases of the bones, 733.
——cause of abnormal bone metabolism, 752.
——composition, 737.
——experiments in osteomalacia, 744.
———calcium, 744.
———comparison of calcium balance in three stages of disease, 748.
———intake and outgo of calcium oxid and magnesium oxid, 746, 747.
———magnesium, 745.
———sulphur, 745.
———ten day observation, 745.
——experiments in rickets, 748.
——introduction to, 733.
——osteitis deformans, 751.
——osteomalacia, acid action in, 752.
———histological examination, 750.
———puerperal, need of calcium as a cause of, 756.
———relation of ovaries to, 754.
——rickets, histological examination, 749.
——summary of observations, 751.
—in diseases of the joints, 772.
——arthropathies secondary to infections, 773.
——classification of arthropathies, 772.
——gout, 772.
——primary atrophic arthritis, 773.
———tables showing results of observations on, 775, 776, 777.
——primary hypertrophic arthritis, 773.
———table of nine-day observations on, 774.
——trophic arthropathies secondary to disease of central nervous system, 772.
—in diseases of respiration and circulation, 541.
——arterial blood, 546.
——blood gases, 546.
——constituents of urine, 549.
Metabolism, in diseases of respiration and circulation, effects on, of oxygen lack, 542.
——gaseous exchange, 545, 546.
——inorganic salts, 551.
——non-volatile products of metabolism in blood and urine, 549.
——oxidative processes, 545.
——pathological effects due to oxygen lack, 542.
——qualitative and quantitative changes, 545.
——reduction of normal reserve, 544.
——respiratory quotient, 545.
——variety of ways affected, 541.
——venous blood, 547.
—and edema, cell, 166.
——inorganic, 166.
——protein, 166.
—effect on, of food, 33.
—energy, in undernutrition, 7.
—error of, see Alkaptonuria.
—in erysipelas, 138.
——analyses of blood and urine, 139.
——respiratory, table, 139.
——total, 138.
—fat, effect on, of oxygen-lack, 544.
——in nephritis, 340.
——in typhoid fever, 109.
——in undernutrition, 10.
—in fever, basal, and Van't Hoff's law, 121.
——caused by parenteral injection of foreign proteins, 144.
——cholera, 147.
——erysipelas, 138.
——experimental, in animals, 150.
——infectious diseases, 148.
———rheumatic fever, acute, 149.
———scarlet fever, 148.
———syphilis, 148.
——introduction to, 95.
——lobar pneumonia, 124.
——malarial, 140.
——observations on, 149, 150.
——toxic and non-toxic, compared, 149.
——tuberculosis, 131.
——typhoid fever, 96.
——Van't Hoff's law and the basal metabolism, 121.
—in gastric diseases, 607.
——atony, 622.
——carcinoma, 619.
——dilatation, 622.
——gastric erosions, 618.
——gastric neuroses, 622.
——gastric ulcer, 618.

Metabolism, in gastric diseases, gastritis, 618.
——gastroptosis, 621.
——influence of variations in diet, 609.
——influence of variations in secretory and motor functions, 610.
——influence of vitamines, 610.
——lues, 621.
——motor disturbances, 614.
————hypermotility, 615.
————motor insufficiency, 615.
————vomiting, 614.
——physiology of gastric digestion, 608.
——pylorospasm, 618.
——polyposis, 621.
——secretory disturbances, 611.
————hypersecretion, hyperchlorhydria, hyperacidity, 611.
————hyposecretion, hypochlorhydria, subacidity, achlorhydria, achylia, 612.
—in gastric disturbances of other diseases, 623.
—in gastric operations, 623.
—glucose, 306.
——disturbances of, glycosuria, 306.
————hyperglycemia, 306.
—in gout, general, 440.
——introduction to, 411.
—hemoglobin pigment, breaking down of hemoglobin, 558.
—in infancy and early childhood, 781.
——disturbances in athreptic infants, 799.
——disturbances due to diminished capacity of certain organ systems, 806.
——disturbances due to an excessive intake of food, 782.
————alkaline condition of intestines, 784.
————breast milk, 788.
————Czerny's classification, 783.
————excess of protein, 786, 787.
————general symptoms, 783.
————infantile diarrhea, 788.
————mineral metabolism, 785.
————pathogenesis of, 783, 786.
————stools in, alkaline, 784.
————————"soap," 783, 785.
——disturbances due to insufficient intake of food, 798.
——disturbances due to insufficiency of certain elements in diet, 802.
————deficiency of carbohydrates, 804.
————deficiency of protein, 804.
Metabolism, in infancy and early childhood, disturbances due to insufficiency of certain elements in diet, edema, 802, 803.
————mineral salts, 805.
————vitamines, 806.
——in exudative diathesis (eczema), 809.
——in infantile diarrhea, 788.
——relationship between amount and quality of food and of weight, 782.
——symptoms coincident with variations in weight curve, 782.
——tetany or spasmophilia, 806.
—in infantilism, achondroplasiac dwarf, table, 827.
——and bone fragility, 820.
——cretin dwarf, table, 828.
——dwarf, type of Lorraine, table, 826.
——fat, 819.
——fat in the feces, 820.
——fatty acids, table, 831.
——intestinal, 814.
————after partial improvement, table, 830.
——introduction to, 813.
——nitrogen in the feces, table, 818.
——nitrogen in the feces and urine, 817, 819.
——nitrogen and sulphur distribution in urine in, 814.
————tables, 815, 816.
——nitrogen in urine and feces, tables, 817, 819.
——tables, 824, 825.
—in infectious diseases of man, miscellaneous, 148.
—inorganic, and edema, 166.
—of inorganic salts, in diseases of respiration and circulation, 551.
—in intestinal diseases, Addison's disease, diarrhea of, 640.
——anchylostomiasis, 636.
——appendicitis, 631.
——carcinoma, 638.
——constipation, 632.
——constituents of intestinal chyme, 626.
——diarrhea of Addison's disease, 640.
——diarrhea of exophthalmic goiter, 640.
——disturbances of motor innervation of intestines, 637.
——disturbances of secretory innervation, 637.
——disturbances of sensibility, 637.

Metabolism, in intestinal diseases, enteritis, acute and chronic, 629.
——enteropathies, congenital, 636.
————due to alterations of lumen or position of intestines, 633.
————neoplastic, 638.
————nervous, 637.
————parasitic, 635.
——enteroptosis, 635.
——exophthalmic goiter, diarrhea of, 640.
——following abnormality of ductless glands, 640.
——functions of intestines, 625.
————absorptive, 628.
————motor, 627.
————secretory, 626.
——inflammatory enteropathies, 629.
——intestinal obstruction, 633.
——introduction to, 624.
——lymphosarcoma, 638.
——mechanical factors, 625.
——motor processes, 627.
——perforation of an ulcer, 631.
——physiological processes of intestines, 624.
——polyposis intestinalis, 638.
——sarcoma, 638.
——secondary to diseases of stomach, 639.
——secretory processes, 626.
——specific, 639.
——syphilis, 639.
——teniasis, 636.
——tuberculosis, 639.
——ulceration of intestines, 630.
——uncinariasis, 636.
—magnesium, 460.
—in malarial fever, calorimetry, direct and indirect, 144.
——character of foodstuffs oxidized, 143.
——chlorids and phosphates, 144.
——temperature regulation in, 141.
——total, 140.
—mineral, in blood diseases, 585.
——iron, influence on, of splenectomy, 596.
——in nephritis, 346.
——in scurvy, 883, 886.
——in undernutrition, 15.
—in nephritis, amino acids, 331.
——carbohydrate, 343.
——chlorid threshold, 363.
——comparative value of uric acid, urea and creatinin in blood, 330.
——creatin, 327.
Metabolism, in nephritis, creatinin, 326.
——fat, 340.
——increased arterial pressure, 397.
——introduction to, 311.
——mineral, 346.
——nephritic toxicosis, 394.
——nitrogen balance, 333.
——non-protein nitrogen of blood and tissues, 319.
——protein, 314.
——protein destruction, 337.
——relation of urea to total non-protein nitrogen of blood, 323.
——renal function, 349.
——in test day for renal function, 372.
——total, 312.
——urea of blood, 321.
——uremia, 382.
—in neuromuscular disease, 707.
——amyotonia congenita, 730.
——glucose supply, 715.
——myasthenia gravis, 730.
——oxygen supply, 709.
——progressive muscular atrophy, 730.
——progressive muscular dystrophy, 720.
——source of energy for muscular contraction, 709.
—nitrogen, in cystinuria, 527.
——dermatoses associated with disturbances of, 702.
——influence on, of splenectomy, 596.
—non-volatile products of, in blood and urine, 549.
—of normal boy, table, 829.
—in obesity, endogenous, 43.
——exogenous, 42.
——of genital origin, 46.
——hypophyseal, 44.
——physiological considerations, 29.
——thyrogenous, 44.
—in pancreatic disease, achylia pancreatica, 674.
——acute toxic necrosis of pancreas —"fat necrosis," 684.
————toxic element in, 688.
——clinical occurrence of creatorrhea and steatorrhea, 678.
——experimental evidence of disturbances of, Abelmann, 658.
————Benedict and Pratt, 661.
————Bernard, Claude (1856), 658.
————Brugsch, 661.
————conclusions on, 662.
————Hildebrand and Dettner, 662.

Metabolism, in pancreatic disease, experimental evidence of disturbances of, Abelmann, Jansen's, 661.
———— Lombroso, 660.
———— McClure, Vincent and Pratt, 662.
———— Minkowski, and von Mering and Minkowski, 659.
———— Niemann, 661.
———— Pratt, Lamson and Marks, 661, 662.
———— Pratt and Spooner, 661.
———— Rosenberg, 659.
———— Sandmeyer, 659.
———— Visentini, 661.
———— Zunz and Mayer, 659.
—— fractional composition of fecal matter, 679.
—— hypochylia pancreatica, 674.
—— malignant tumors, 671.
—— or obstruction of ducts, diagnosis resting on basis of clinical tests, 664.
———— fat and nitrogen excretion, tables, 669, 670, 671.
———— fatty stool, 664, 665.
———— muscle fiber in feces (creatorrhea), 664, 665.
———— observations on, 665-671.
———— obstructive jaundice, 663.
———— pancreatic calculus and its sequel, 670.
———— question of accessory duct taking over the function of main duct, 664.
———— question of patency of ducts after attempts at artificial production of a complete blockage of pancreatic secretion, 663.
———— testing for presence of pancreatic ferments, 664.
—— opotherapy, 682.
—— pancreatic infantilism, 681.
—— pancreatic insufficiency, 674.
—— physiological considerations, 657.
—— theory of an internal secretion of pancreas that controls food absorption, 675.
— in pathological conditions of stomach and intestines, 607.
—— See also Metabolism, in gastric diseases: and Metabolism, in intestinal diseases.
— phosphorus, 458.
— in pneumonia (lobar), 124.
—— acidosis, 130.
—— basal, 125.
—— blood constituents, 129.
Metabolism, in pneumonia, chlorid, 127.
—— miscellaneous metabolites, 130.
—— nitrogen excretion, 126.
— in pregnancy, normal, table of, 844.
—— pathological, 835.
———— blood examination by modern methods, 848.
———— changes of urea nitrogen in blood, 854.
———— cholesterol content of blood, 858.
———— creatin in blood, 855.
———— creatinin in blood, 855.
———— eclampsia, tables of, 844, 845, 851.
———— eclampsia and albuminuria, 835.
———— eclampsia and liver involvement, 836.
———— eclampsia, and theories of cause of, 838.
———— examination of urine by modern methods, 839.
———— glycosuria, 857.
———— hepatic toxemia, table, 853.
———— historical, 835.
———— nitrogen in the blood, 851.
———— nitrogen partition, 839.
———— pancreatic insufficiency, 858.
———— summary of, 858.
———— uric acid nitrogen in blood, increase of, 857.
———— urine in experimental liver necrosis, 842.
———— urine in, further studies of, 843.
———— urobilinogen or urobilin in urine, 858.
— protein, in anaphylaxis, 209.
—— in anemia, 574.
—— and edema, 166.
—— effect on, of oxygen-lack, 543.
—— in leukemia, 578.
—— in nephritis, 314.
—— in typhoid fever, 111.
—— in undernutrition, 12.
— purin, in anemia, 579.
—— in leukemia, 579.
— relation of dermatoses to disturbances of, 693.
—— associated with carbohydrate metabolism, 703.
———— with cardiovascular disease, 699.
———— with diet, 697.
———— with digestive disturbances, 695.

Metabolism, relation of dermatoses to disturbances of, associated with carbohydrate metabolism, with disturbed nitrogen metabolism, 702.
— — — with endocrin disturbances, 701.
— — — with miscellaneous causes, 703.
— — — with nervous diseases, 700.
— — — with renal disease, 700.
— — — with respiratory diseases, 701.
— relation of, to oxygen supply, see Oxygen supply.
— relation to, of sexual glands, 754.
— respiratory, in anaphylaxis, 212.
— in rheumatic fever, acute, 149.
— in scarlet fever, 148.
— in scurvy, of animals, 885.
— — blood examination, 885.
— — complicated by rickets, 884.
— — historical, 883.
— — mineral, 883, 886.
— — nitrogen, 886.
— in shock, basal, 257.
— in syphilis, 148.
— in test day for renal function, 372.
— total, in typhoid fever, 98.
— in tuberculosis, 131.
— — blood constituents, 138.
— — character of foodstuffs oxidized, 134.
— — effect of food, 135.
— — sputum, 134.
— — table of McCann and Barr, 132.
— — temperature regulation, 136.
— — total, 132.
— in typhoid fever, 96.
— — body weight, 119.
— — calorimetry, direct and indirect, 100.
— — carbohydrate, 109.
— — effect of food, 116.
— — — absorption, 117, 118.
— — — specific dynamic action of, 118.
— — fat, 109.
— — protein, 111.
— in typhoid fever, regulation of body temperature, 101.
— — respiratory quotient, 106.
— — surface temperature, 105.
— — total, 98.
— — urinary constituents, 120.
— — water metabolism, 106.
— in undernutrition, body weight, 16.
— — breaking fast, 25.
— — carbohydrate, 10.
— — cause of death, 25.
— — energy, 7.
Metabolism, in typhoid fever, fat, 10.
— — mineral, 15.
— — physiology, of circulatory system, 19.
— — — of digestive system, 18.
— — — disposition and mental balance, 22.
— — — of excretory system, 21.
— — — mental capacity, 22.
— — — of muscular system, 17.
— — — of nervous system, 21.
— — — reproductive system, 23.
— — — of respiration, 21.
— — protein, 12.
— — possible duration of fasting, 24.
— — therapeutic use of fasting, 26.
— — water, 4.
— water, in typhoid fever, 106.
— — in undernutrition, 4.
Metabolites, miscellaneous, in pneumonia, 130.
Milk, cow's, feeding of or of whey of, in infantile diarrhea, effects of, 795.
Mineral metabolism, in blood diseases, 585.
— — phosphoric acid, calcium and magnesium, 589.
— — sulphur, 591.
— in hemorrhage, 586.
— in infancy and early childhood, 785.
— in infantilism, 820.
— iron, influence on, of spleen, 596.
— in nephritis, chlorids of the blood, 346.
— — phosphates and calcium of the blood, 348.
Mineral metabolism, in scurvy, 883.
— in undernutrition, 15.
Mineral salts, metabolic disturbances in infancy and early childhood due to insufficiency of, 805.
Mineral substances, in bile, 649.
Molecular concentration, of edema fluids, 162.
Mongolianism, see Infantilism.
Morphin, in treatment of gout, 453.
Motor activity of intestines, and metabolism, 627.
Motor disturbances of stomach, metabolism in, 614.
— — hypermotility, 615.
— — motor insufficiency, 615.
— — vomiting, 614.
Motor insufficiency of stomach, metabolism in, 615.
Motor innervation of intestines, disturbances of, metabolism in, 637.

Multiple myeloma, and Bence-Jones protein, metabolic study of Hopkins and Savory, table, 492, 493.
——metabolic study of Seegelken, table, 495, 496.
——metabolic study of Walters, tables, 496, 497, 498.
——myelopathic proteosuria (Kahler's disease), 498.
Muscle fiber, in feces, in pancreatic disease, 664, 665.
Muscle power, influence on, of glucose, 715.
Muscles, effect on, of anaphylaxis, 204.
Muscular atrophy, progressive, metabolism in, 730.
—secondary to chronic arthritis, blood sugar in, 722.
Muscular contraction, source of energy for, 709.
——glucose supply, 715.
——oxygen supply, 709.
Muscular dystrophy, progressive, see Progressive muscular dystrophy.
Muscular system, physiology of, in undernutrition, 17.
Muscular weakness, due to inadequate or non-utilizable food supply, 715.
Myasthenia gravis, metabolism in, 730.
Myelopathic proteosuria, 498.

Necrosis, liver, experimental, urine in, 842.
—of the pancreas, acute toxic, "fat necrosis," 684.
————toxic element in, 688.
Nephritic toxicosis, 394.
—and edema of the brain, 394.
—possible cause of, cholin and neurin, 396.
——nephrolysins, 396.
——organic base, 396.
——sodium chlorid, 395.
——trimethylamin, 395.
—summary of, 396.
Nephritides, gastric disturbances in, and metabolism, 623.
Nephritis, acidosis in, 313.
——diagnosis of, 90.
——therapy for, 90.
——type and cause of, 89.
—amino acids in, 331.
—blood lipoids in, 341.
—carbohydrate metabolism in, blood sugar, 343.
——utilization of carbohydrates, 343.
—chlorid threshold in, 363.
——Atchley's observations, 365.
Nephritis, chlorid threshold in, formulæ of Ambard and Weil, 364.
——McLean's observations, 365.
——other investigations on, 366.
—cholesterol content of blood in, 342.
—clinical application in, 313.
—comparative value of uric acid, urea and creatinin in blood in, 330.
—creatin in, 327.
—creatinin in, 326.
—dyspnea in, 312.
—edema in, 312.
——Epstein's dietetic therapy of, 191.
——treatment of, 189.
—factors in, 311.
——degenerative changes, 311.
——inflammatory changes, 311.
——renal insufficiency, 311.
—fat metabolism, analyses of Bloor, table, 341.
——blood lipoids, 341.
——cholesterol content of blood, 342.
——lipemia, 342.
——lipuria (chyluria), 340.
——utilization of fat in nephritis, 340.
—high blood pressure in, 313.
—increased arterial pressure in, 397, 398.
——acute nephritis, 398.
——cause of, 401.
————blood volume and plethora, 402.
————epinephrin, 404.
————increased vasomotor tone, 403.
————insufficient renal function, 401.
————internal secretions derived from kidney, 405.
————viscosity of blood, 402.
——chronic diffuse (parenchymatous) nephritis, 399.
——essential hypertension and primary contracted kidney, 400.
——influence on, of food products, 406.
——nephrosis, 398.
——occurrence of, 398.
——and secondary contracted kidney, 399.
—lipemia in, 342.
—lipuria in, 340.
—metabolism in, amino acids, 331.
——analysis of human muscle, normal and nephritis, 320.
——analysis of tissue in nephritis, 321.
——carbohydrate, 343.
——chlorid threshold, 363.

Nephritis, metabolism in, comparative value of uric acid, urea and creatinin in blood in, 330.
— — creatin, 327.
— — creatinin, 326.
— — during test day for renal function, 372.
— — fat, 340.
— — increased arterial pressure, 397.
— — introduction to, 311.
— — mineral, 346.
— — nephritic toxicosis, 394.
— — nitrogen balance, 333.
— — non-protein nitrogen of blood and tissues in, 319.
— — protein, 314.
— — protein destruction, 337.
— — relation of urea to total non-protein nitrogen of blood, 323.
— — renal function, 349.
— — total, 312.
— — urea of blood, 321.
— — uremia, 382.
— mineral metabolism in, chlorids of the blood, 346.
— — phosphates and calcium of the blood, 348.
— nephritic toxicosis accompanying, see Nephritic toxicosis.
— nitrogen balance in, 333.
— — determination of, 336.
— — effect of renal injury, 335.
— — factors in, 333.
— — fate of ingested nitrogen, 334.
— — misleading, 335.
— — table, 334.
— problems of, 312.
— protein destruction in, 337.
— protein metabolism in, 314.
— — utilization of proteins, 314.
— in its relation to edema, 174.
— — acute diffuse, 175.
— — chronic diffuse, 176.
— — chronic interstitial, 175.
— — chronic parenchymatous, 176.
— — subacute, 176.
— relation of urea to total non-protein nitrogen of blood, 323.
— and renal function, 313, 349.
— — chlorid threshold, 363.
— — coefficient of urea excretion, 357.
— — concentration and dilution test, 381.
— — lactose test, 357.
— — and laws of urea excretion, 360.
— — phthalein test, 350.
— — potassium iodid test, 357.
— — Schlayer's theories of, 355.
Nephritis, and renal function, test day for, 368.
— — tests for, 350.
— — tests for function of the glomeruli and tubules, 353.
— total metabolism in, 312.
— — acidosis, 313.
— — clinical application, 313.
— — and dyspnea, 312.
— — and edema, 312.
— — high blood pressure, 313.
— — rate of, 313.
— — renal function, 313.
— urea of blood in, 321.
— uremia, 382.
— — causative agents of, possible, 389.
— — conditions of ten erroneously classified as, 387.
— — definition of, 382.
— — as described by Cohnheim, Julius, in 1882, 384.
— — division of, into groups, 387.
— — introduction to, 382.
— — more recent aspects of, 387.
— — symptom-complex dependent upon renal insufficiency, 388.
— utilization of proteins in, 314.
Nephrolysins, as cause of nephritic toxicosis, 396.
Nervous diseases, dermatoses associated with, 700.
Nervous enteropathies, metabolism in, 637.
Nervous system, effect on, of undernutrition or fasting, 21.
— in obesity, 36.
Neurin, as cause of nephritic toxicosis, 396.
Neuromuscular disease, metabolism in, 707.
— — amyotonia congenita, 730.
— — glucose supply, 715.
— — myasthenia gravis, 730.
— — oxygen supply, 709.
— — progressive muscular atrophy, 730.
— — progressive muscular dystrophy, 720.
— — source of energy for muscular contraction, 709.
Neuropathic edema, 158.
Neuroses, gastric, metabolism in, 622.
New growths, as cause of diabetes insipidus, 864.
Nitrogen, in the blood, in pregnancy, 851.

Nitrogen, creatinin, in blood, in pregnancy, 855.
— cystin, in proteins, 519.
— excreted in urine, in fasting man, 13.
— — in pneumonia lobar, 126.
— in feces, in infantilism, intestinal, 818.
— in feces and urine, in infantilism, 817, 819.
Nitrogen, non-protein, in blood and tissues in nephritis, 319.
— and salt, elimination of, in test day for renal function, 377.
— urea, in blood, in pregnancy, changes in, 854.
— uric acid, in blood, in pregnancy, increase of, 857.
— in urine and feces, in infantilism, tables, 817, 819.
Nitrogen balance, in anemia, 574.
— in leukemia, 578.
— negative, in typhoid, table showing, 115.
— in nephritis, 333.
— — determination of, 336.
— — effect of renal injury, 335.
— — factors in, 333.
— — fate of ingested nitrogen, 334.
— — misleading, 335.
— — table, 334.
Nitrogen distribution in urine in infantilism, 814.
— — tables, 815, 816.
Nitrogen elimination and intake, in typhoid fever, 111.
Nitrogen equilibrium, bringing normal man into, 115.
— in typhoid fever, food required to bring patients into, 116.
Nitrogen hunger, Landergren's method of determining changes in nitrogen metabolism, 148.
Nitrogen metabolism, in anaphylaxis, 212.
— in cystinuria, 527.
— dermatoses associated with disturbances of, 702.
— influence on, of splenectomy, 596.
— in scurvy, 886.
Nitrogen minimum, "wear and tear quota" of Rubner, 114.
Nitrogen partition, in anemia, 583.
— — hemolytic, 584.
— in chlorosis, 584.
— in pathological metabolism of pregnancy, 839.
— in pernicious anemia, 584.
Nitrogenous constituents of urine, effect on partition of, of anemia, 583.
Nitrogenous metabolites and fats of blood, chemical changes in, 592.
Nocturnal polyuria, in test day for renal function, 374.
Nucleic acid, characteristic constituents of, 415.
— formation from, of uric acid, 419.
— hydrolytic products of, 416.
— purin bodies disintegration products of, 415.
— synthesis of uric acid and, 421.
Nucleic acids, animal and plant, 416.
Nuclein, 415.
Nucleoproteins, 415.
Nutrition, borderline malnutrition, 250, 251.
— cereal products in, degerminated and decorticated, 245.
— — diet consisting solely of, 244, 246.
— diet consisting solely of cereal grains, 244, 246.
— diets successful in, types of, 245.
— effects of undernutrition, 247.
— — Aron's experiments, 247.
— — other observations on, 248.
— experimental observations of effects on, of deficient diets, 243.
— ideal of, during period of growth, 242.
— important changes in viewpoint relating to, 243.
— and vitamines, 242.
Nutritional processes, 239.
— requirements of, 239.
— — food constituents, 239.
— synthesization of complex organic compounds from simple one, 240.
Nycturia, in test day for renal function, 377.

Obesity, adiposis dolorosa or Dercum's disease, 40.
— and the adrenal gland, 39.
— clinical description of, 33.
— definition of, 29.
— endogenous, definition of, 37.
— — genital, 39.
— — metabolism in, 43.
— — treatment of, 49.
— exogenous, 34.
— — factors in, age, 34.
— — — heredity, 34.
— — — race, 34.
— — — sex, 34.
— — metabolism in, 42.
— — other detrimental effects of, 36.

Obesity, exogenous, relation of, to diabetes, 36.
———to gout, 36.
——symptomatology of, 34.
————alimentary tract, 35.
————circulation, 34.
————kidneys, 35.
————liver, 35.
————lungs, 35.
————nervous system, 36.
————pancreas, 35.
————sexual apparatus, 35.
——treatment of, 47.
—fasting in treatment of, 27.
—genital origin of, metabolism in, 46.
—hypophyseal, metabolism in, 44.
—of hypophyseal origin, 37.
—lipomatosis distinguished from, 36.
—metabolism in, in endogenous form, 43.
——in exogenous form, 42.
——in genital form, 46.
——in hypophyseal form, 44.
——in thyrogenous form, 44.
—physiological considerations of, 29.
—and pineal gland, 39.
—thyrogenous, 37.
——metabolism in, 44.
—treatment of, in endogenous form, 49.
——in exogenous form of, 47.
Obstruction of the bowels, metabolism in, 633.
Obstructive jaundice, causing decalcification of bones, 761.
—concomitant to obstruction of pancreatic duct, 663.
Ochronosis, relationship between alkaptonuria and, 514.
Opotherapy, in pancreatic disease, 682.
"Optimal" caloric diets in diabetes, 285.
Osmosis, 184.
Osmotic pressure, in lymph production and edema, 184.
Osteitis deformans, and arteriosclerosis, 765.
—causes of, 765.
—histological examination in metabolism study of, 751.
Osteogenesis imperfecta, process in, 765.
Osteomalacia, and adrenal glands, 766.
—and arteriosclerosis, 761.
—composition of bones in, 738.
——calcium oxid percentage, 738, 739.
——magnesium percentage, 739.
————disproportionate increase of, in artificial osteomalacia, 741.
Osteomalacia, composition of bones in, magnesium oxid percentage, 740.
——magnesium phosphate percentage, 740.
——phosphate percentage, 739.
——sulphur percentage, 743.
—due to deficiency of calcium in diet, 764.
—due to negative calcium balance induced by oxalic acid or oxalates in food, 768.
—and hypophysis, 767.
—induced by glucose injections, 768.
—induced by lactose injections, 768.
—metabolism in, acid action, 752.
——during different stages of, 770, 771.
—histological examination, 750.
——summary of observations, 751.
—metabolism experiments in, 744.
——calcium, 744.
——calcium balance, comparison of, in three stages of disease, 748.
——intake and outgo of calcium oxide and magnesium oxide in, 746, 747.
——magnesium metabolism, 745.
——sulphur metabolism, 745.
——ten day observation, 745.
—and oxalic acid or oxalates in food, 768.
—and parathyroid glands, 767.
—puerperal, castration in, 755, 759.
——chemical evidence on, 756.
——clinical evidence on, 757.
——fetus in, 757.
——histological investigations on, 757.
——need of calcium as a cause of, 756.
——summary of evidence on, 758, 759.
—relation of ovaries to, 754.
—relation of, to rickets, 734.
—spontaneous, in animals, due to calcium-poor diet, 764, 765.
—and thyroid glands, 766.
—transmittable infectious agent, in, 766.
Osteoporosis and acromegaly, 761.
Ovaries, relation of, to osteomalacia, 754.
Oxalate, formation of, 464.
—resorption of, in digestive canal, 463.
Oxalates, in food, negative calcium balance and osteomalacia due to, 768.
Oxalate calculi, dietetic and medicinal treatment of, 470.
Oxalic acid, excretion of, 464.

Oxalic acid, exogenous sources of, 463.
— in food, negative calcium balance and osteomalacia due to, 768.
— formation of, 463.
— — and creatin, 464.
— in urine, 463.
Oxaluria, definition of, 462.
— diet scheme in, 471.
Oxidative processes, in diseases of respiration and circulation, 545.
Oxygen content of blood in heart failure, 172.
Oxygen-lack, effects of, 542.
— — acidosis, 544.
— — emergency compensations, 542.
— — incomplete combustion, 543.
— — — of carbohydrates, 543.
— — — of fats, 544.
— — — of proteins, 543.
— — lactic acid, 543.
— — on metabolism, 542.
Oxygen supply, relation of, to metabolism, facts on, 714.
— — misconceptions of, 709.
— — — Krehl, 709.
— — — Lusk, 709.
— — — pathological conditions attributed to incomplete oxidation, 710.
— — — place of oxidation, 712.
— — — source of, in Lavoisier's writings, 711.
— — new theories of, 713.
— — — credit for, 714.
— — — Pflüger, 713, 714.
— — — Voit, 712, 713, 714.
— — place of oxidation, correct and incorrect theories of, 712.

Pancreas, acute toxic necrosis of—"fat necrosis," 684.
— — toxic element in, 688.
—experimental extirpation of, Abelmann, 658.
— — Benedict and Pratt, 661.
— — Bernard, Claude, 658.
— — Brugsch, 661.
— — conclusions on, 662.
— — Hildebrand and Dettner, 662.
— — Jansen, 661.
— — Lombroso, 660.
— — McClure, Vincent and Pratt, 662.
— — Minkowski, and von Mering and Minkowski, 659.
— — Niemann, 661.
— — Pratt, Lamson and Marks, 661, 662.
— — Pratt and Spooner, 661.
— — Rosenberg, 659.
Pancreas, experimental extirpation of, Sandmeyer, 659.
— — Visentini, 661.
— — Zunz and Mayer, 659.
— functions of, 657.
— — interference with, by disease, 658.
— internal secretion of, that controls food absorption, 675.
— — nature of, 276.
— malignant tumors of, 671.
— — fat and nitrogen excretion in, table, 671.
— — metabolism in, 671.
— nature of, 657.
— necrosis of, acute toxic—"fat necrosis," 684.
— — toxic element in, 688.
— in obesity, 35.
— secretion of, 657.
— theory of an internal secretion of, that controls food absorption, 675.
Pancreatic calculus, and its sequel, 670.
Pancreatic disease, creatorrhea, clinical occurrence of, 678.
— fecal matter in, fractional composition of, 679.
— metabolism in, acute toxic necrosis of pancreas—"fat necrosis," 684.
— — — toxic element in, 688.
— — experimental evidence of disturbances of Abelmann, 658.
— — — Benedict and Pratt, 661.
— — — Bernard, Claude (1856), 658.
— — — Brugsch, 661.
— — — conclusions on, 662.
— — — Hildebrand and Dettner, 662.
— — — Jansen, 661.
— — — Lombroso, 660.
— — — McClure, Vincent and Pratt, 662.
— — — Minkowski, and von Mering and Minkowski, 659.
— — — Niemann, 661.
— — — Pratt, Lamson and Marks, 661, 662.
— — — Pratt and Spooner, 661.
— — — Rosenberg, 659.
— — — Sandmeyer, 659.
— — — Visentini, 661.
— — — Zunz and Mayer, 659.
— — fractional composition of fecal matter, 679.
— — malignant tumors, 671.
— — opotherapy, 682.
— — pancreatic infantilism, 681.
— — pancreatic insufficiency (achylia pancreatica, hypochylia pancreatica), 674.

Pancreatic disease, metabolism in, physiological considerations, 657.
——theory of an internal secretion of the pancreas that controls food absorption, 675.
—opotherapy in, 682.
—prognosis of, 683.
—signs of, clinical, 676.
—steatorrhea, clinical occurrence of, 678.
—stools in, 676, 677.
——fractional composition of, 679.
——See also Creatorrhea and Steatorrhea.
—or obstruction of ducts, metabolism in, diagnosis resting on basis of clinical tests, 664.
————fat and nitrogen excretion, tables, 669, 670, 671.
————fatty stool, 664, 665.
————muscle fiber in feces (creatorrhea), 664, 665.
————observations on, 665-671.
————obstructive jaundice, 663.
————pancreatic calculus, and its sequel, 670.
————question of accessory duct taking over the function of main duct, 664.
————question of patency of ducts after attempts at artificial production of a complete blockage of pancreatic secretion, 663.
————testing for presence of pancreatic ferments, 664.
Pancreatic duct, closed, fat and nitrogen excretion in, 669.
Pancreatic ferments, testing for presence of, in stool, urine, blood and duodenal or stomach contents, 664.
Pancreatic infantilism, metabolism in, 681.
Pancreatic insufficiency, metabolism in, 674.
—in pregnancy, 858.
Pancreatitis, acute, fat and nitrogen excretion in, 669.
—chronic, fat and nitrogen excretion in, 670.
Parasitic enteropathies, metabolism in, 635.
Parathyroid glands, and disturbances of bone metabolism, 767.
Parenteral injection of foreign proteins, fever caused by, 144.
Pellagra, bacteriology of, 905.
—clinical course of, 904.
—definition of, 899.
Pellagra, diagnosis of, 906.
—etiologic relationship between beriberi and, theory of, 900.
—etiology of, age, 902.
——geographical distribution, 901.
——race, 902.
——regional incidence, 902.
——relation to, of diet, 901.
————of food, 903.
——sewage, 903.
——sex, 902.
——social status, 902.
——specific, 899.
——and theories of dietary deficiency, 900.
—experimental inoculation, 904.
—geographical distribution, 901.
—pathological anatomy of, 904.
—pathological chemistry of, 905.
—prophylaxis of, 906.
—relation of diet to cause and treatment of, 911.
—treatment of, 907.
——relation to, of diet, 911.
Pemphigus, associated with miscellaneous causes, 705.
Pentose, derivation of, 295.
—distribution of, 292, 295.
—variety of, found, 294.
Pentosuria, alimentary, 292.
—essential, causation of, 293.
——diagnosis of, 293.
——distribution of pentose, 295.
——occurrence of, 292.
——variety of pentose found, 294.
Peptones, 483.
Peptonuria, 483.
Perforated intestinal ulceration, metabolism in, 631.
Pernicious anemia, gastric disturbances in, and metabolism, 623.
—metabolism in, basal, 568.
——influence on, of splenectomy, 598.
—mineral metabolism in, phosphoric acid, calcium and magnesium, 590.
—nitrogen partition in, 584.
—treatment of, by splenectomy, influence of, on metabolism, 598.
Phagocytosis, process of, 554.
Phenylcinchoninic acid, action of, in gout, 438.
Phosphate, percentage of, in bone ash, 740.
——in dried bone, 740.
Phosphate balance, in pregnancy, 757.
Phosphate calculi, dietetic and medicinal treatment of, 468.

Phosphate stones and phosphaturia, 458.
Phosphates of the blood, in nephritis, 348.
— in malaria, 144.
Phosphaturia, cardinal symptoms of, 458.
— endogenous, 460.
— — changes in urine during, 460.
— — etiological division of, 460.
— — origin of, 462.
— — symptoms combined with, 460.
—and phosphate stones, 458.
Phosphoric acid metabolism, in blood diseases, 589.
Phosphorus metabolism, 458.
Phthalein test for renal function, 350.
— clinical significance of, 351.
— technic of, 351.
Pineal gland, and obesity, 39.
Pituitrin, in treatment of diabetes insipidus, 877.
Plasma bicarbonate, gasometric determination of, 79.
— titrimetric determination of, 80.
Plethora, and arterial hypertension, 402.
Pneumonia, influenzal, blood chemistry findings in, 131.
— lobar, acidosis in, 130.
— — blood constituents in, 129.
— — metabolism in, 124.
— — — acidosis, 130.
— lobar, metabolism in, miscellaneous metabolites, 130.
— — — blood constituents, 129.
— — — chlorid, 127.
— — — nitrogen excretion, 126.
— — — basal, 125.
Polyposis, gastric, metabolism in, 621.
Polyposis intestinalis, metabolism in, 638.
Polyuria, nocturnal, in test day for renal function, 374.
Potassium, as causative agent of uremia, 391.
Pregnancy, calcium and phosphate balance during, 757.
— as cause of diabetes insipidus, 866.
— — normal table of, 844.
— — pathological, 835.
— — — blood examination by modern methods, 848.
— — — changes of urea nitrogen in blood, 854.
— — — cholesterol content of blood, 858.
— — — creatin in blood, 855.
Pregnancy as cause of diabetes insipidus, pathological, creatinin in blood, 855.
— — — eclampsia, and albuminuria, 835.
— — — — and liver involvement, 838.
— — — — tables of, 844, 845, 851.
— — — — and theories of cause of, 836.
— — — — examination of urine by modern methods, 839.
— — — glycosuria, 857.
— — — hepatic toxemia, table, 853.
— — — historical, 835.
— — — nitrogen in the blood, 851.
— — — nitrogen partition in, 839.
— — — pancreatic insufficiency, 858.
— — — summary of, 858.
— — — uric acid nitrogen in blood, increase of, 857.
— — — urine in, further studies of, 843.
— — — urine in experimental liver necrosis, 842.
— — — urobilinogen or urobilin in urine, 858.
Pressure, in lymph production and edema, diffusion, 183.
— — — of the solute, 184.
— — — of the solvent, 184.
— — electrostatic, 187.
— — hydrostatic, 181.
— — osmotic, 184.
Progressive muscular atrophy, 730.
— alkalosis in, 724.
— — with creatinuria, 724.
— — with hypoglycemia, 724.
— blood sugar in, 721.
— creatinuria in, 723.
— — with alkalosis, 724.
— as an endocrin disease, 728.
— glucose administered intravenously in, 722.
— hypocholesterinemia in, 724.
— — delayed glucose utilization, 725.
— — fatty infiltration, 726.
— hypoglycemia in, 720.
— — with alkalosis, 724.
— metabolism in, 730.
— — carbohydrate, 720.
— — — alkalosis, 724.
— — — creatinuria, 723.
— — — hypocholesterinemia, 724.
— — — hypoglycemia, 720.
— parallelism between improvement in strength and rise in blood sugar in, 722.
Protein, Bence-Jones, see Bence-Jones Protein.

Protein, deficiency of, in metabolic disturbances of infancy and childhood, 804.
— deficient in diet, interference of, with growth, 246.
— excess of, in diet of infancy and early childhood, 786, 787.
— in food supply of diabetes, 283.
— as source of glucose supply, 271.
Protein constituents, of edema fluids, 160.
— of lymph, normal, 160.
Protein destruction, as cause of uremia, 393.
— in nephritis, 337.
Protein intoxication, 230.
Protein metabolism, in anaphylaxis, 209.
— in anemia, 574.
— — hemolytic, 576.
— and edema, 166.
— effect on, of oxygen-lack, 543.
— in leukemia, 578.
— in nephritis, 314.
— in typhoid fever, 111.
— in undernutrition, 12.
Protein poisoning, edema due to, 158.
Protein starvation, 13.
Proteins, blood, possible derivation from, of Bence-Jones protein, 488.
— cystin in, 518.
— cystin nitrogen in, 519.
— foreign, parenteral injection of, fever caused by, 144.
— and the liver, 645.
— utilization of, in nephritis, 314.
Proteose relationships, of Bence-Jones protein, 488.
Proteoses, in urine, 483.
Proteosuria, and Bence-Jones protein, 487.
— myelopathic, 498.
— types of, 483.
Protocatechinic acid, in urine of alkaptonurics, 503.
Pruritus, associated with angioneurotic edema, 697.
Prurigo, associated with diet, 698.
— — with miscellaneous causes, 705.
Psoriasis, associated with miscellaneous causes, 705.
Ptosis of the stomach, metabolism in, 621.
Puerperal osteomalacia, chemical evidence on, 756.
— clinical evidence on, 758.
— fetus in, 757.
— histological investigations on, 757.
Puerperal osteomalacia, need of calcium as a cause of, 756.
— summary of evidence on, 758, 759.
Pulse rate, average, in fasting man, 20.
— — in underfeeding, 20.
Purgatives, in treatment of edema, 193.
Purin bodies, and formulæ for, 412.
— and nucleic acid, 415.
Purin-containing food, effect of, on output of uric acid, 423.
Purin-free diet, for uric acid calculi, 469.
Purin metabolism, in anemia, 579.
— in leukemia, 579.
Pylorospasm, metabolism in, 618.
Pyrocatechol, in urine of alkaptonurics, 503.

Race, as factor in obesity, 34.
— as factor in pellagra, 902.
Radium, influence of, on metabolism, in blood diseases, 601.
Radium emanations in treatment of gout, 454.
Renal calculi, and colloidal material, 457.
— constituents of concretions, 457.
— formation of concretions, 457.
— metabolic studies of, calcium metabolism, 459.
— — cystin calculi, 468.
— — magnesium metabolism, 460.
— — oxaluria and oxalate calculi, 462.
— — phosphaturia and phosphate stones, 458.
— — phosphorus metabolism, 458.
— — uraturia and uric acid calculi, 465.
— — xanthin calculi, 467.
— See also Urinary calculi.
Renal disease, dermatoses associated with, 700.
Renal excretory function in its relation to edema, 174.
— nephritis, acute diffuse, 175.
— — chronic diffuse, 176.
— — chronic interstitial, 175.
— — chronic parenchymatous, 176.
— — subacute, 176.
— renal function in other conditions associated with edema, 178.
— summary of, 178.
Renal function, 349.
— and laws of urea excretion, clinical value of coefficiency of urea excretion, 362.

Renal function, and laws of urea excretion, concentration of urea in urine, 361.
——— effect of concentration of urea in blood on quantity of urea excreted by kidneys, 360.
——— method of determining the coefficient of urea excretion, 362.
——— relation of water elimination to urea excretion, 361.
——— reliability of coefficients of urea excretion, 362.
— in nephritis, 313.
— Schlayer's theories of, in nephritis, 355.
— test day for, 368.
——— criteria for judging efficiency of kidney by means of, 371.
——— criteria of value, summary of, 378.
——— degrees of variation of specific gravity, 371.
——— tables of, 371, 372, 373, 374, 375.
——— diet in, normal, 370.
——— table showing, 378.
——— dietary for, 369.
——— directions for, 370.
——— elimination of salt and nitrogen, 377.
——— maximal specific gravity, 374.
——— metabolism in, 372.
——— nocturnal polyuria, 374.
——— tables of, 375, 376.
——— nycturia, 377.
— tests for, 350.
——— coefficient of urea excretion, 357.
——— Ambard's coefficient, 358.
——— Austin, Stillman and Van Slyke, 360.
——— McLean's, 359.
——— concentration and dilution, 381.
——— table of, 382.
——— function of the glomeruli and tubules, 353.
——— lactose, 357.
——— phthalein test, 350.
——— potassium iodid, 357.
——— for urea and salt excretion, 366.
Renal injury, effect of, on nitrogen balance in nephritis, 335.
Renal insufficiency, as cause of increased arterial pressure in nephritis, 401.
— symptoms produced by, 388.
— uremia depending upon, 388.
Renal stones, causing disturbed bone metabolism, 761.
Renal theory of gout, 441.
Respiration, cell, and edema, 166.
Respiration and circulation, diseases of, metabolism in, 541.
——— arterial blood, 546.
——— blood gases, 546.
——— constituents of urine, 549.
——— effects on, of oxygen lack, 542.
——— gaseous exchange, 545, 546.
——— inorganic salts, 551.
——— non-volatile products of metabolism in blood and urine, 549.
——— oxidative processes, 545.
——— pathological effects due to oxygen lack, 542.
——— qualitative and quantitative changes, 545.
——— reduction of normal reserve, 544.
——— respiratory quotient, 545.
——— variety of ways affected, 541.
——— venous blood, 547.
— harmonious interaction between systems of, 544.
Respiratory diseases, dermatoses associated with, 701.
Respiratory metabolism, in anaphylaxis, 212.
— in erysipelas, 139.
Respiratory quotient, in diseases of respiration and circulation, 545.
— in typhoid fever, 106.
Respiratory regulation of free H_2CO_3 of the blood, 64.
Respiratory system, effect on, of undernutrition or fasting, 21.
Reproductive system, effect on, of fasting and undernutrition, 23.
Retroflexion of uterus, gastric disturbances in, and metabolism, 623.
Retention uremia, 388.
Rheumatic fever, acute, metabolism in, 149.
Rickets, in breast fed children, 249.
——— cause of, 250.
— causes of, 765.
— complicating scurvy, 884.
— composition of bones in, change in, 743.
— due to deficiency of calcium in diet, 764.
—histological examination in, 749.
— metabolism in, summary of observations, 751.
— metabolism experiments in, 748.
— relation to, of osteomalacia, 734.
— transmittable infectious agent in 766.

Röntgen-rays, influence of, on metabolism, in blood diseases, 601.
— in treatment of blood diseases, influence of, on metabolism, 601.
Rosacea, associated with diet, 698.
— — with miscellaneous causes, 705.

Salicylates, in treatment of gout, 454.
Salt and nitrogen, elimination of, in test day for renal function, 377.
Salt excretion, tests for, 366.
Sarcoma of the intestines, metabolism in, 638.
Scarlet fever, metabolism in, 148.
Schlayer's theories of renal function in nephritis, 355.
Schmidt diet, 674.
Scurvy, in breast-fed children, 249.
— cause of, 250.
— metabolism in, of animals, 885.
— — blood examination, 885.
— — complicated by rickets, 884.
— — historical, 883.
— — mineral, 883, 886.
— — nitrogen, 886.
Seborrhea, associated with miscellaneous causes, 703, 705.
Secretory disturbances, metabolism in, hyperacidity, hyperchlorhydria, hypersecretion, 611.
— — hyposecretion, hypochlorhydria, subacidity achlorhydria, achylia, 612.
Secretory innervation of intestines, disturbances of, metabolism in, 637.
Secretory processes of intestines, and metabolism, 626.
Sella turcica, and diabetes insipidus, 870.
Sensibility of intestines, disturbances of, metabolism in, 637.
Serum disease, blood coagulation in, 221.
— clinical picture of, 218.
— definition of, 219.
— factors concerning development and recovery from, 221.
— incubation period of, 219.
— mechanism causing, 221.
— reactions in, accelerated, 220.
— — immediate, 220.
— — normal, 219.
— — types of, 219.
— tissue changes in, 220.
Sex, as factor in cystinuria, 524.
— — in diabetes insipidus, 863.
— — in obesity, 34.
— — in pellagra, 902.
Sex impulses, effect on, of fasting and undernutrition, 23.
Sexual apparatus, in obesity, 35.
Sexual evidences of diabetes insipidus, 870.
Sexual glands, relation of, to metabolism, 754.
Shock, acidosis in, 256.
— basal metabolism in, 257.
— chemical blood changes in, 258.
— traumatic, see Traumatic shock.
Skin, in edema, 156.
Sodium chlorid, as causative agent of nephritic toxicosis, 395.
— as causative agent of uremia, 391.
Sodium chlorid content of plasma in heart failure, 173.
Soda-edema, 158.
Sodium monourate, deposition of, in gout, 439.
Spasmophilia, infantile, 806.
Spleen, influence of, on iron metabolism, 596.
— regulatory influence of, in blood formation and destruction, 562.
Splenectomy, in blood diseases, influence of, on metabolism, 596.
— influence of, on metabolism, in blood diseases, 596.
— — clinical observations, 597.
— — experimental observations, 596.
Sputum, in tuberculosis, 134.
Starvation, Allen method of, in diabetes, 26.
— cause of death from, 25.
— duration of life in, with and without water, 5.
— in epilepsy, therapeutic use of, 27.
— percentage loss of body weight in, 24.
— percentage loss in weight of various organs in, 18.
— water, see Water starvation.
— See also Fasting; and Undernutrition.
Steatorrhea, clinical occurrence of, 678.
Stomach, diseases of, metabolism in, see Gastric diseases, metabolism in.
— function of, 608.
— metabolism in diseases of, 607; see also Gastric diseases, metabolism of.
Stomach contents, pancreatic ferments in, testing for presence of, 664.
Stools, fatty, in pancreatic disease, 664, 665.
— in metabolism disturbances of infancy, alkaline, 784.
— — "soap," 783, 785.

Stools, in pancreatic disease, 676, 677.
— — fractional composition of, 679.
— — See also Steatorrhea and Creatorrhea.
— pancreatic ferments in, testing for presence of, 664.
Subacidity, metabolism in, 612.
Sugar, in edema fluids, 162.
Sugar excretion, total of, fermentable and unfermentable, 265.
Sugars, other than glucose in diabetic urine, 267.
Sulphur, amount of, in bone, 743.
— in cystin, 515.
Sulphur distribution in urine in infantilism, 814.
— tables, 815, 816.
Sulphur excretion, in fasting, 14.
Sulphur metabolism, in blood diseases, 591.
— in osteomalacia, 745.
Sulphur partition in cystinuria, 534.
Suprarenal secretion, as cause of arterial hypertension in nephritis, 404.
Surface area, Meeh formula for determining, 31.
Syphilis, as cause of diabetes insipidus, 866.
— of the intestines, metabolism in, 639.
— metabolism in, 148.

Tabes dorsalis, gastric disturbances in, and metabolism, 623.
Taurin, cystin a precursor of, 518.
Temperature of the body, regulation of, in typhoid fever, 101.
— — in malaria, 141.
— — in tuberculosis, 136.
— surface, in typhoid fever, 105.
— — in undernutrition, 7.
— — tables, 8.
— influence of, on solubility of acid sodium urate, 466.
Teniasis, metabolism in, 636.
Test day for renal function, 368.
— — criteria for judging efficiency of kidney by means of, 371.
— — criteria of value, summary of, 378.
— — degrees of variation of specific gravity, 371.
— — — tables of, 371, 372, 373, 374, 375.
— — diet in, normal, 370.
— — — — — table showing results of, 378.
— — dietary for, 369.
— — directions for, 370.
— — elimination of salt and nitrogen, 377.
Test day for renal function, maximal specific gravity, 374.
— — metabolism in, 372.
— — nocturnal polyuria, 374.
— — — tables, 375, 376.
— — nycturia, 377.
Tests for renal function, coefficient of urea excretion, 357.
— — concentration and dilution, 381.
— — — table of, 382.
— — function of the glomeruli and tubules, 353.
— — lactose, 357.
— — phthalein, 350.
— — potassium iodid, 357.
— for urea and salt excretion, 366.
Tetany, infantile, and metabolism, 806.
Therapeutics, fasting in, 26.
Thymus gland, relation of, to bone and calcium metabolism, 767.
Thyrogenous obesity, 37.
— metabolism in, 44.
Thyroid gland, relation between disturbances of bone metabolism and, 766.
— rôle of, in edema, 167.
Thyroid therapy, for edema, 193.
— — contra-indications to, 193.
— — indications for, 193.
Tissue retention theory of gout, 442.
Tissues, subcutaneous, in edema, 156.
— uric acid in, in gout, 435.
— uric acid in organs and, 426.
Total metabolism, in typhoid fever, 98.
Toxemia, hepatic, table, 853.
Toxemias, of pregnancy, urine in, further studies of, 843.
Toxic fevers, metabolism in, 149.
Toxicosis, nephritic, see Nephritic toxicosis.
Toxins, in infantile diarrhea, theory of, 796.
Transfusion, in blood diseases, influence of, on metabolism, 594.
— influence of, on metabolism, in blood diseases, 594.
Transudates, see Edema, fluids of.
Trauma, as cause of diabetes insipidus, 865.
Traumatic shock, acidosis in, 256.
— characteristic picture of, 253.
— chemical blood changes in, 258.
— definition of, 253.
— metabolism in, basal, 257.
— occurrence of, 253.
— pathological physiology of, 254.
— sequence of events in, 259.

Traumatic shock, summary of, 259.
— theories of, 254.
— treatment of, 260.
— types of, primary and secondary, 253.
Trimethylamin, and nephritic toxicosis, 395.
Tuberculosis, blood constituents in, 138.
— character of foodstuffs oxidized in, 134.
— effect of food in, 135.
— of intestines, metabolism in, 639.
— metabolism in, 131.
— — blood constituents, 138.
— — character of foodstuffs oxidized, 134.
— — effect of food, 135.
— — temperature regulation, 136.
— temperature regulation in, 136.
— sputum in, chemistry of, 134.
— — table of McCann and Barr, 132.
— — total, 132.
Tumors of the pancreas, malignant, see Pancreas, malignant tumors of.
Typhoid fever, metabolism in, urinary constituents, 120.
— — body weight, 119.
— effect of food in, 116.
— — specific dynamic action, 118.
— — absorption of, 117, 118.
— metabolism in, 96.
— — calorimetry, direct and indirect, 100.
— — carbohydrate, 109.
— — fat, 109.
— — nitrogen balance in, 112.
— — protein, 111.
— — regulation of body temperature, 101.
— — respiratory quotient, 106.
— — surface temperature, 105.
— — total, 98.
— — water, 106.
— nitrogen equilibrium in, food required to bring patients into, 116.
— nitrogen balance in, 112.
— — chart showing, 115.
— table of averages in, 98.
Tyrosin, transformation of, to homogentisic acid, in urine of alkaptonurics, 507.
— in urine, conditions causing, 476.
— — in cystinuria, 527.

Ulceration of intestines, metabolism in, 630.
Uncinariasis, metabolism in, 636.
Undernutrition, breaking fast, 25.
— carbohydrate metabolism in, 10.
— cause of death in starvation, 25.
— causes of, 3.
— condition of, 3.
— effects of, on physiology, blood pressure, 20.
— — of circulatory system, 19.
— — of digestive system, 18.
— — excretory system, 21.
— — kidneys, 21.
— — mental balance and disposition, 22.
— — mental capacity, 22.
— — of muscular system, 17.
— — nervous system, 21.
— — pulse rate in fasting man and in underfeeding, 20.
— — reproductive system, 23.
— — respiration, 21.
— energy metabolism in, body temperature, 7.
— — — tables, 8.
— — heat production, 8.
— fat metabolism in, 10.
— metabolism in, body weight, 16.
— — — percentage loss in weight of various organs in starvation, 18.
— — possible duration of fasting, 24.
— mineral metabolism in, 15.
— modified form of starvation, 4.
— problems of, 3.
— protein metabolism in, 12.
— starvation, with and without water, 5.
— therapeutic use of fasting and, 26.
— voluntary fasting, 4.
— water metabolism in, 4.
— — storage of water, 7.
— — water balance in fasting man, table, 6.
— — water starvation, 5.
— — — See also Fasting; and Starvation.
Uraturia, and acid sodium urate, 465, 466.
— definition of, 465.
Urea, of blood, in nephritis, 321.
— as causative agent of uremia, 389.
— in nephritis, comparative value of uric acid, creatinin and, in blood, 330.
— in urine, concentration of, 361.
Urea excretion, coefficient of, 357.
— — Ambard's, 358.
— — Austin, Stillman and Van Slyke, 360.
— — clinical value of, 362.
— — McLean's, 359.

Urea excretion, coefficient of, method of determining, 362.
——— reliability of, 362.
— laws of, and renal function, clinical value of coefficiency of urea excretion, 362.
——— concentration of urea in urine, 361.
——— effect of concentration of urea in blood on quantity of urea excreted by kidneys, 360.
——— method of determining the coefficient of urea excretion, 362.
——— relation of water elimination to urea excretion, 361.
——— reliability of coefficients of urea excretion, 362.
— relation to, of water elimination, 361.
— tests for, 366.
Urea nitrogen, in blood, in pregnancy, changes of, 854.
Ureids, 412.
Uræmia, causative agents of, possible, acidosis, 391.
——— creatin, 390.
——— creatinin, 390.
——— disturbed water metabolism, 393.
——— indicanemia, 391.
——— potassium, 391.
——— protein destruction, 393.
——— sodium chlorid, 391.
——— urea, 389.
——— uric acid, 391.
— conditions hitherto often erroneously classified as, 387.
— definition of, 382.
— as described by Cohnheim, Julius, in 1882, 384.
— division of, into groups, 387.
——— conditions hitherto often erroneously classified as uremia, 387.
——— symptom-complex depending upon renal insufficiency (retention uremia), 388.
— introduction to, 382.
— more recent aspects of, 387.
— retention, 388.
— summary of, 396.
Uric acid, in the blood, in gout, 428.
——— in health, 425.
— as causative agent of uremia, 391.
— decomposition products of, 414.
— effect on output of, of purin-containing food, 423.
— elimination of, in leukemia, 581.
— formation of, from nucleic acid, 419.
— formula for, 413.
Uric acid, and gout, 411.
— in the joint exudates, in gout, 434.
— in nephritis, comparative value of urea, creatinin and, in blood, 330.
— in the organs, 426.
— and purin bodies, 412.
— relation of, to alantoin, 414.
——— to purin bodies, 413.
— source of, in the urine, 422.
— synthesis of, 414.
— synthesis of nucleic acid and, 421.
— in the tissues, 426.
——— in gout, 435.
Uric acid calculi, 465.
— dietetic and medicinal treatment of, 468.
Uric acid (combined) theory of gout, 442.
Uric acid nitrogen in blood, in pregnancy, increase in, 857.
Urinary calculi, beginning of, 457.
— constituents of, 457.
— cystin, metabolic study of, 468.
— dietetic and medicinal treatment of, cystin calculi, 472.
— dietetic and medicinal treatment of, oxalate calculi, 470.
——— phosphate calculi, 468.
——— uric acid calculi, 468.
——— xanthin calculi, 472.
— metabolic studies of, calcium metabolism, 459.
——— cystin calculi, 468.
——— magnesium metabolism, 460.
——— oxaluria and oxalate calculi, 462.
——— phosphaturia and phosphate stones, 458.
——— phosphorus metabolism, 458.
——— uraturia and uric acid calculi, 465.
——— xanthin calculi, 467.
— oxalate, metabolic study of, 462.
— phosphate, metabolic studies of, 458.
— uric acid, metabolic study of, 465.
— xanthin, metabolic study of, 467.
Urinary changes, in phosphaturia, 460.
Urinary constituents, in typhoid fever, 120.
Urine, acetone bodies in, determination of, 84.
— in alkaptonuria, see Alkaptonuria, urine of.
— amino acid nitrogen in, amount found by various investigators, table, 475.
— amino acids in, increased amount of, in pathological conditions, or amino-aciduria, 475.
— analysis of, in erysipelas, 139.

Urine, Bence-Jones protein in, 486.
— black, in alkaptonuria, 501.
— Cammidge reaction in, 305.
— constituents of, in relation to diseases of respiration and circulation, 549.
— cystin in, detection and separation of, 522.
— — other nitrogenous substances present together with, 525.
— diabetic, heptose in, 304.
— — sugars other than glucose in, 267.
— fructose in, concentration of, 298.
— glucose in, 264.
— glycuronic acid in, 405.
— — Cammidge reaction, 305.
— in gout, 436.
— heptose in, 304.
— in infantile diarrhea, 793.
— leucin in, in cystinuria, 527.
— in liver necrosis, experimental, 842.
— maltose in, 303.
— nitrogen in feces and, in infantilism, 817, 819.
— nitrogen and sulphur distribution in, in infantilism, 814.
— — — tables, 815, 816.
— nitrogenous constituents of, effect of anemia on partition of, 583.
— non-volatile products of metabolism in, 549.
— oxalic acid in, 463.
— pancreatic ferments in, testing for presence of, 664.
— proteoses in, 483.
— reducing substances of, 264.
— — total, 264.
— in toxemia of pregnancy, further studies of, 843.
— tyrosin in, in cystinuria, 527.
— urea in, concentration of, 361.
— uric acid in, source of, 422.
— urobilinogen or urobilin in, in pregnancy, 858.
— xanthin in, 467.
Urinol, as cause of nephritic toxicosis, 396.
Urobilin, amount of, in urine, estimations of, 562.
— origin of, 561.
Urobilin in urine in pregnancy, 858.
Urobilinogen in urine, in pregnancy, 858.
Uroleucic acid, in urine of alkaptonurics, 503.
Urticaria, associated, with diet, 698.
— — with digestive disturbances, 697.
— — with miscellaneous causes, 705.
— due to protein poisoning, 158.

Van't Hoff's law and basal metabolism in fever, 121.
Vasomotor tone, increased, and arterial hypertension in nephritis, 403.
Venous blood, observations on, 547.
Vitamines, importance given to, 242.
— metabolic disturbances in infancy and early childhood due to deficiency of, 806.
— relation of, to bone metabolism, 769.
— rôle of, in dietetic treatments of certain digestive diseases, 610.
— therapeutic use of, 242.
— in treatment of beriberi, 894.
Vomiting, of children, cyclic, see Cyclic vomiting of children.
— metabolism in, 614.

War edema, 158.
Water balance, of fasting man, table, 6.
Water metabolism, disturbed, as cause of renal insufficiency, 393.
— storage of water, 7.
— in typhoid fever, 106.
— in undernutrition, 4.
Water starvation, 4.
— critical level in order to avoid, 5.
— symptoms of, 5.
Weight of the body, in fasting man, 16.
— — percentage loss in weight of various organs in starvation, 18.
— percentage loss of, in starvation, 24.
— in typhoid fever, 119.

Xanthin, chemical nature of, 468.
— formula for, 413.
— in urine, 467.
Xanthin calculi, 467.
Xanthoma, associated with miscellaneous causes, 705.

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